Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000336

International filing date: 24 March 2005 (24.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/555,667
Filing date: 24 March 2004 (24.03.2004)

Date of receipt at the International Bureau: 18 April 2005 (18.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT/IL2005/000336
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APPLICATION NUMBER: ***60/555,667***
FILING DATE: ***March 24, 2004***

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FEE RECORD SHEET

03/25/2004 BSAYASI1 00000086 60555667
01 FC:1005 160.00 OP

PTO-1556.
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

16698 U.S. PTO
032404

22264 U.S. PTO
60/555667

PTO/SB/16 (01-04)
Approved for use through 07/31/2006. OMB 0651-0032
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Express Mail Label No.

INVENTOR(S)

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Additional inventors are being named on the one *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

METHODS OF SCREENING FOR ANTI-VIRAL DRUGS AND THEIR PHARMACEUTICAL COMPOSITIONS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 108
☑ Drawing(s) *Number of Sheets* 2
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

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FILING FEE Amount ($): 160.00

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☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

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Date March 21, 2004

REGISTRATION NO. *(if appropriate)*

Docket Number:

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METHODS OF SCREENING FOR ANTI-VIRAL DRUGS AND THEIR PHARMACEUTICAL COMPOSITIONS.

FIELD OF THE INVENTION

The present invention relates in general to the field of drug screening, more particularly to screening of drugs for the treatment of diseases that involve deleterious virus-cell adhesion, virus attachment, entry and virus infection. Specifically, the present invention relates to methods for screening, identification and optimization of small organic molecules that inhibit virus attachment to cells mediated by glycosaminoglycans, and use thereof for the treatment of viral diseases. The present invention relates also to pharmaceutical composition comprising compounds capable of inhibiting the interactions between glycosaminoglycans (GAGs), particularly heparan sulfate glycosaminoglycans (HS-GAGs) and GAG-binding viral proteins (GBVPs).

BACKGROUND OF THE INVENTION

The extracellular matrix (ECM) has an important function in providing structural integrity to tissues and in presenting appropriate environmental cues for cell adhesion, migration, growth, and differentiation. Major constituents of ECM include glycosaminoglycans (GAGs), fibronectin, laminin, collagen and proteoglycans, which mediate and drive specific cell surface receptor-ligand interactions. Many protozoa, bacteria and viruses have been shown to bind cell surface GAGs. Viruses have evolved to exploit the cell-surface GAGs, particularly Heparan Sulfate (HS)-GAGs, to facilitate their attachment and infection of host cells. A growing body of evidence points to the role of cell surface HS-GAGs as the initial receptor in viral infection.

Glycosaminoglycans

Glycosaminoglycans (also referred to herein and in the art as "GAG" or "GAGs") are naturally-occurring carbohydrate-based molecules implicated in the regulation of a number of cellular processes, including blood coagulation, angiogenesis, tumor growth and smooth muscle cell proliferation, most likely by interaction with effector molecules. GAGs are linear, non-branched chains of repeating two-sugar (disaccharide) units, which may be up to 150 units in length

(Kjellen et al. (1991) Ann. Rev. Biochem. 60:443-475).

Glycosaminoglycans can be divided into four main classes on the basis of a repeating disaccharide unit in the backbone. Typically, one sugar is an uronic acid, and the other is either an N-acetylglucosamine or an N-acetylgalactosamine. The classes are exemplified by the following GAGs: (1) heparan sulfate (D-glucuronic acid/N-acetyl- or N-sulfo-D-glucosamine); (2) chondroitin/dermatan sulfate (D-glucuronic acid or L-iduronic acid/N-acetyl-D-galactosamine); (3) keratan sulfate (D-galactose/N-acetyl-D-glucosamine); and (4) hyaluronic acid (glucuronic acid/N-acetyl-D-glucosamine). All GAGs (with the exception of hyaluronic acid) contain sulfate groups variously esterified to the ring hydroxyl groups of the sugars. These negatively charged groups are believed to figure prominently in the biological properties attributed to glycosaminoglycans. The naturally occurring forms of GAGs, particularly heparin, heparan sulfate, chondroitin sulfate and dermatan sulfate are, in fact, complex hetero-oligosaccharides composed of mixtures of differentially sulfated sugar residues. One of the most thoroughly studied glycosaminoglycans is the widely used anticoagulant heparin. Heparin, a highly sulfated form of heparan sulfate, is found in mast cells. Overall, heparin is less abundant than related sulfated polysaccharides, such as heparan sulfate, dermatan sulfate, and chondroitin sulfate, which are synthesized in nearly all tissues of vertebrates. As a commercial product, heparin is a hetero-oligodisaccharide composition of about 20-60 monomeric units. Heparan sulfate glycosaminoglycans (also referred to herein and in the art as "HS-GAGs") consist of repeating disaccharide units. Relatively small segments of HS-GAGs contain disaccharide units that are the actual binding sites for ligands (usually 3–10 disaccharides out of 40–160 disaccharides). The specificity of the GAG biosynthetic enzymes imposes restrictions on the disaccharide GAG sequence. HS-GAG chains typically contain regions rich in GlcA and GlcNAc (N-Acetylated domains), contiguous variable length sequences containing GlcNS derivatives (N-Sulfated domains), and some sections that contain alternating N-Acetylated and N-Sulafted units of glucosamine. Typical HS-GAG chains contain relatively short segments of modified sequences interspersed among large sections of unmodified units. Interestingly, the relative content of N-Acetylated, N-Sulfated, and N-Acetylated/N-Sulfated domains as well as other properties of the chains appears to be a stable characteristic of the cells from which the HS-GAG was obtained (Esko JD and Selleck SB 2002 Annu. Rev. Biochem. 71, 435-71).

HS-GAG chains are assembled while they are attached to a proteoglycan core protein. Heparan Sulfate Proteoglycans (HS-PGs) are ubiquitous macromolecules associated with the cell surface and the ECM of a wide range of cells of vertebrate and invertebrate tissues. The basic HS-PG structure consists of a protein core to which several linear heparan sulfate chains are covalently attached. Three major families of proteoglycan core proteins have been characterized: the membrane-spanning syndecans (four members), the glycosylphosphatidylinositol-linked glypicans (six members), and the basement membrane PGs perlecan and aggrin. Several other HS-GAG -bearing proteoglycans are known as well (e.g., betaglycan and a CD44 splice variant). The syndecans can contain up to five GAG chains whereas glypicans typically contain one to three HS chains. The different core proteins are expressed in a cell-type-specific manner. Studies on the involvement of ECM molecules in cell attachment, growth and differentiation revealed a central role of HS-PGs in embryonic morphogenesis, angiogenesis, metastasis, neurite outgrowth and tissue repair.

Infectious Viruses Attach to and Enter Cells via binding to GAGs

A growing body of evidence points to the role of cell surface GAGs as the initial receptor in viral infection. Specifically, viruses such as Herpes Simplex Virus (HSV), Dengue Virus (Chen, Y. et al., 1997, Nature Med. 3, 866-871), Respiratory Syncytial Virus (Krusat T. and Strecken HJ, 1997, Arch. Virol. 142, 1247-1254), Varicella-zoster virus (VZV; Jacquet, A., 1998, Virus Res. 53,197-207), Cytomegalovirus (Compton, T. et al., 1993, Virology 193, 834-841), Sindbis Virus, Adeno-associated Virus, Vaccinia Virus, Foot -and-mouth Disease Virus and HIV-1 (Saphire AC et al, 1999, EMBO J 18:6771-6785) all employ HS-GAGs for their initial step of infection. The infectivity of these viruses may be inhibited in vitro by pretreatment of cultured cells with heparitinase prior to the infection, or by addition of exogenous GAGs such as heparin or HS-GAG, or by addition of polysulfated compounds such as suramin (Chen et al., 1997, ibid). The crystal structure of the complex between foot-and-mouth disease virus and HS has been elucidated (Fry EE et al., 1999, EMBO J. 18, 543-554). Although the mechanism of attachment has been elucidated in only a few cases, it is probably mediated by electrostatic interactions between basic protein domains (e.g., heparin-binding domains) on the surface of viruses and the sulfated HSPG side

chains. In the case of HSV-1 entry, an essential role for 3-O-sulfated glucosamine residues on HS has been demonstrated (Shukla D. et al., 1999, Cell 99, 13-22). This indicates that the interactions between viral proteins and HS are very specific. Although HS-GAG serves as an initial receptor for the binding of both herpes simplex virus type 1 (HSV-1) and HSV-2 to cell surfaces, the two serotypes differ in epidemiology, cell tropism, and ability to compete for viral receptors in vitro (Herold BC et al, 1996, J Virol 70:3461-9). These observations are not necessarily contradictory and can be explained if the two serotypes recognize different structural features of HS-GAG. It was found that the antiviral activity of heparin for both serotypes was independent of anticoagulant activity. Moreover, specific negatively charged regions of the HS-GAGs, including N sulfations and the carboxyl groups, are key structural features for interactions of both HSV-1 and HSV-2 with cell surfaces since N desulfation or carboxyl reduction of heparin abolished its antiviral activity. In contrast, 6-O sulfations and 2-3-O sulfations are important determinants primarily for HSV-1 infection. The O-desulfated heparins had little or no inhibitory effect on HSV-1 infection but inhibited HSV-2 infection. It was found that susceptibility to O-desulfated heparins can be transferred to HSV-1 by the gene for glycoprotein C of HSV-2 (gC-2). This supports the notion that the envelope glycoproteins of HSV-1 and HSV-2 interact with different affinities for different structural features of heparin. To determine if the modified heparin compounds inhibited plaque formation by competing with cell surface HS-GAG for viral attachment, binding studies were also performed. As anticipated, most compounds inhibited binding and plaque formation in parallel, but subtle differences were determined. These results suggest differences in the interactions of HSV-1 and HSV-2 with cell surface HS-GAG that may influence cell tropism. It was confirmed recently that wild-type strains of HSV-1 bind to GAGs. Viruses derived from clinical specimens were, similar to their cell culture propagated progeny viruses, sensitive to heparin. In addition, wild-type HSV-1 infection of HS deficient cells was also impaired (Trybala E et al, 2002, Virology 302:413-9).

After causing childhood chickenpox, VZV remains latent in nerve tissues, held in check by the immune system. It remains there until the immune system is compromised, perhaps as a consequence of stress, illness or just old age. At such times, the virus may reactivate causing shingles particularly in the elderly and presenting as a painful strip of vesicles, usually around the trunk, with the risk of

severe, chronic pain and persistent after-effects. VZV causes shingles outbreaks on 3.5 million sufferers in the West each year, with as many as 95% of the world's adult population carrying VZV. The risk of contracting shingles increases with age. There is a shortage of efficient drugs for VZV infections. Current antiviral pharmaceuticals include acyclovir and valaciclovir, which exert an effect on the vesicles that erupt, but only a marginal effect on chronic pain. A broad selection of analgesic drugs and pain killers are used against the chronic pain, with varying results.

Protozoa and Bacteria use GAGs to Attach to and Infect Cells

A feature of infection by Plasmodium falciparum (malaria) is the ability of parasite-infected erythrocytes to adhere to vascular endothelial cells and accumulate in vital organs, associated with severe clinical disease. The GAG, Hyaluronic acid, was identified as a receptor for adhesion and has been implicated in mediating the accumulation of parasites in the placenta (Beeson JG et al, 2002, Int J Parasitol. 32:1245-52). The mammalian receptors for B. burgdorferi, the spirochete that causes Lyme disease, include glycosaminoglycans (Coburn J, 2002, 14:394-8). Potent inhibition of Chlamydia trachomatis serovar L2 was observed when elementary bodies (Ebs) were exposed to heparin or when HeLa 229 cells were treated with heparinase. This and additional evidence published by Yabushita et al, suggest that infection of host cells by EBs results from the specific binding of ligand molecules with affinity for heparin on the EB surface to HS on the surface of the host cells (Yabushita H et al, 2002, Glycobiology 12:345-51).

GAG-BindingViral Proteins (GBVPs)

Recent data have identified a host of virus-specific proteins which interact with HS-GAGs. The first example, Herpes simplex virus type 1 (HSV-1), binds to cells through interactions of viral glycoproteins gB and gC with heparan sulfate chains of cell surface proteoglycans (Laquerre et al, 1998 J Virol. 72:6119-30). This binding is necessary, but not sufficient for viral entry, which requires fusion between the viral envelope and cell membrane. It was shown that HS-GAG, modified by a subset of the multiple D-glucosaminyl 3-O-sulfotransferase isoforms, provides sites for the binding of a third viral glycoprotein, gD. The interaction between gD and its receptor may stabilize the virus-cell complex prior to membrane fusion which is mediated by other

essential glycoproteins such as gB, gH, and gL (Tal-Singer et al 1995, J Virol. 69:4471-4483). and for initiation of HSV-1 entry. It was concluded that the susceptibility of cells to HSV-1 entry depends on (1) the presence of heparan sulfate chains to which virus can bind and (2) 3-O-sulfation of specific glucosamine residues in heparan sulfate to generate gD-binding sites or the expression of other previously identified gD-binding receptors.

HS-GAG has an important role in cell entry by foot-and-mouth disease virus (FMDV). Subtype O1 FMDV binds this GAG with high affinity by immobilizing a specific highly abundant motif of sulfated sugars. The binding site is a shallow depression on the virion surface, located at the junction of the three major capsid proteins, VP1, VP2 and VP3. Two pre-formed sulfate-binding sites control receptor specificity. Residue 56 of VP3, an arginine in this virus, is critical to this recognition, forming a key component of both sites. This residue is a histidine in field isolates of the virus, switching to an arginine in adaptation to tissue culture, forming the high affinity heparan sulfate-binding site. It is postulated that this site is a conserved feature of FMDVs, such that in the infected animal there is a biological advantage to low affinity, more selective, interactions with GAG receptors.

Cell surface heparan sulfate serves as an initial receptor for a number of herpesviruses including pseudorabies virus (PrV). It has been demonstrated that the heparan sulfate-binding domain of PrV glycoprotein C is composed of three discrete clusters of basic residues corresponding to amino acids 76-RRKPPR-81, 96-HGRKR-100, and 133-RFYRRGRFR-141, respectively, and that these clusters are functionally redundant, i.e. each of them could independently support PrV attachment to cells (Flynn, S. J., and Ryan, P. (1996) J. Virol. 70, 1355-1364). To evaluate the functional significance of each of these clusters PrV mutants were used in which, owing to specific alterations in glycoprotein C, the heparan sulfate-binding site was dominated by a single specific cluster. These mutants exhibited different patterns of susceptibility to selectively N-, 2-O-, and 6-O-desulfated heparin preparations in virus attachment/infectivity assay. Moreover PrV mutants differed with regard to efficiency of their attachment to and infection of cells pretreated with relatively low amounts of heparan sulfate-degrading enzymes. Glycoprotein C species, purified from respective mutants, were also found to bind heparin oligosaccharide fragments of different

minimum size. These differences suggest that specific clusters of basic amino acids of the heparan sulfate-binding domain of glycoprotein C may support PrV binding to different structural features/stretches within the heparan sulfate chain.

In an attempt to identify the human herpesvirus 7 (HHV-7) envelope protein(s) involved in cell surface binding, the extracellular domain of the HHV-7 glycoprotein B (gB) homolog protein was cloned and expressed as a fusion product with the Fc domain of human immunoglobulin G heavy chain gamma1 (gB-Fc) in a eukaryotic cell system (Secchiero P et al 1997, J Virol 71:4571-80). Indirect immunofluorescence followed by flow cytometric analysis revealed specific binding of gB-Fc to the membrane of SupT1 cells but not to other CD4+ T-lymphoblastoid cell lines, such as Jurkat or PM1, clearly indicating that gB-Fc did not bind to the CD4 molecule. This was also suggested by the ability of gB-Fc to bind to CD4-negative fibroblastoid Chinese hamster ovary (CHO) cells. The binding was abrogated by enzymatic removal of cell surface heparan sulfate proteoglycans by heparinase and heparitinase but not by treatment with condroitinase ABC. In addition, binding of the gB-Fc fusion protein to CHO cells was severely impaired in the presence of soluble heparin, as well as when heparan sulfate-deficient mutant CHO cells were used. Consistent with these findings, soluble heparin was found to block HHV-7 infection and syncytium formation in the SupT1 cell line. Although the CD4 antigen is a critical component of the receptor for the T-lymphotropic HHV-7, these findings suggest that heparin-like molecules also play an important role in HHV-7-cell surface interactions required for infection and that gB represents one of the HHV-7 envelope proteins involved in the adsorption of virus-to-cell surface proteoglycans.

HIV-1 attachment to host cells is generally considered to take place via high-affinity binding between CD4 and gp120. However, the binding of virion-associated gp120 to cellular CD4 is often weak, and most cell types that are permissive for HIV-1 infection express little CD4. Thus, other interactions between the virion and the cell surface could dominate the attachment process. It has been shown that host cell cyclophilin is incorporated into the viral particle at a rate of 200 molecules/particle, and cyclophilin binding via a basic heparin-like domain to HS mediates HIV-1 attachment and infectivity (Saphire AC et al, 1999 EMBO J. 18, 6771-6785). In the case of Dengue virus, infectivity depends on its envelope protein where two basic

putative GAG-binding motifs were identified at its carboxy-terminus (Chen, Y. et al., 1997, Nature Med. 3, 866-871). Respiratory Syncytial Virus infection is mediated by the attachment of fusion glycoprotein F to HS (Feldman, SA, et al., 2000, J. Virol. 74, 6442-6447). Attachment of human Cytomegalovirus (CMV) at the cell surface is rapid and efficient in permissive as well as non-permissive cell types, suggesting that cellular receptors for CMV are widely distributed. Addition of exogenous heparin or the treatment of cells with heparinase blocks viral attachment and implicates the proteoglycan heparan sulfate in the initial interaction between virus and cell. For human CMV it was shown that the envelope glycoproteinB(gB) is an important mediator of virus entry that works, at least in part, via heparin sulfate binding (Boyle KA and Compton T 1998, J Virol. 72, 1826-1833).

While some clinical benefit in ameliorating the sequelae of viral infection has been achieved by treatment with nucleoside analogues and interferons, therapy with both types of compounds can involve significant side effects. Patients treated with acyclovir, for example, may exhibit local inflammation at sites where the drug is administered, renal dysfunction, and encephalopathic changes. Experience in the use of vidarabine has revealed neurologic toxicity. Patients treated with interferon may exhibit fever, fatigue, anorexia, weight loss, nausea and vomiting, bone marrow suppression, pain at injection sites, lymphadenopathy, and mild hair loss. There thus exists a need in the art for additional products useful in preventing or treating viral infection.

The present invention relates also to pharmaceutical composition comprising compounds with anti-viral activity. US Patent No. 5,783,577 discloses the synthesis of quinazolinone libraries and derivatives thereof. The disclosed compounds are different from the compounds of the present invention as they do not possess a methylthio group at position 2 of the quinazolinone ring. SciFinder Scholar database lists 328 derivatives (as of February 24, 2004) of 2-methylthio-7-quinazolinecarboxamides of general Formula I described herein below, but no utility or chemical synthesis data are described. Nowhere in the background art is it taught or suggested that 2-methylthio-7-quinazolinecarboxamides have beneficial pharmaceutical activities.

SciFinder Scholar database lists 310 compounds (as of February 24,2004) of the general Formula II described herein below, but no utility or chemical synthesis data are described.

SciFinder Scholar database lists 13 substances (as of February 24,2004) of 2-methylthioquinazolines of the general Formula III described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database lists 161 derivative (as of February 24, 2004) of thiazolidineacetic acid of the general Formula IV described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database lists 319 derivatives (as of February 24, 2004) of benzothiazolium of the general Formula V described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database lists 2 derivatives (as of February 24, 2004) of thienothiazolium of the general Formula VI described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database lists 2 derivatives (as of February 24 ,2004) of benzimidazolium of the general Formula VII described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database lists 1 derivative (as of February 24, 2004) of thiazolideneethanesulfonic acid of the general Formula VIII described herein below, but no utility or chemical synthesis data is described.

SciFinder Scholar database, release 2002, lists 454 derivatives (as of December 25, 2002) of 3,5-disubstituted 2-thioxo-4-thiazolidinone of general Formula IX described herein below, but no utility or chemical synthesis data is described.

Nowhere in the background art is it taught or suggested that compounds of the general formula I - X have beneficial pharmaceutical activities.

SUMMARY OF THE INVENTION

The present invention is directed to methods for the screening, identification and use of small organic molecules that modulate interactions and signaling events mediated by glycosaminoglycans (GAGs), particularlly adhesion events between GAGs and viruses and more specifically between GAGs and specific GAG-Binding Viral Proteins (GBVPs). It is an object of some aspects of the present invention to

provide pharmaceutical compositions comprising small organic compounds for medical and diagnostic use, wherein the small organic compounds are inhibitors of the interactions between GAGs and viruses and more specifically between heparan sulfate and specific GBVPs. Accordingly, these compositions are useful as inhibitors of virus attachment and entry. In addition, the compositions interact directly with HS-GAGs and are therefore useful as inhibitors of any HS-GAG mediated processes and conditions.

According to one aspect the present invention provides a method of screening for small organic molecules that directly inhibit the interaction of GAGs with virus proteins, the method comprising the steps of:

a. contacting a GAG with a GBVP in the presence of at least one candidate compound;
b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as an Inhibitor Compound, inhibiting GAG-GBVP interaction.

According to one embodiment, GAG may be immobilized before it is contacted with a GBVP.

According to another embodiment, GBVP may be immobilized before it is contacted with a GAG.

According to yet another embodiment, GAG or GBVP may be tagged or labeled before measuring GAG-GBVP binding. Tagging may be performed by use of a dye, a fluorescent dye, a chemiluminescent agent or a radioactive agent. Tagging of GBVP may be by an antibody directed to the specific GBVP or to a protein fused to the GBVP.

According to one embodiment, the small organic molecules screened by the methods of the present invention interact with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

According to one currently preferred embodiment, the glycosaminoglycans are HS-GAG or heparin or derivatives and oligosaccharide fragments thereof.

According to another embodiment the small compounds screened by the methods of the present invention interact with proteoglycan containing GAG,

particularly heparan sulfate proteoglycan (HS-PG).

According to one embodiment, the small organic molecules screened by the methods of the present invention inhibit the interaction of GAGs with GAG specific GBVPs selected from the group consisting of CMV envelope glycopotein B, hepatitis C envelope protein, etc.

According to one currently preferred embodiment, the small compounds screened by the methods of the present invention inhibit the interaction of GAGs with CMV envelope glycopotein B, particularly, the interaction of the GAG with the heparin binding domains of CMV envelope glycopotein B.

According to some other aspects the present invention provides a pharmaceutical composition comprising as an active ingredient an Inhibitor Compound identified by a screening method comprising the steps of:

a. contacting a GAG with a GBVP in the presence of at least one candidate compound;

b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as an Inhibitor Compound, inhibiting GAG-GBVP interaction,

further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits GAG-GBVP binding by interacting with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

According to one currently preferred embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits GAG-GBVP binding by interacting with HS-GAG or heparin or derivatives and oligosaccharide fragments thereof.

According to another embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits the interaction of GAGs with GBVPs selected from the group consisting of CMV envelope glycoprotein B, etc..

According to one currently preferred embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits the interaction of GAGs with CMV envelope glycoprotein B.

According to yet some other aspects the present invention provides methods for modulation of virus attachment and entry *in vivo* or *in vitro* mediated by interactions of GAGs and specific GBVPs.

According to one embodiment the present invention provides a method for inhibiting virus attachment and entry *in vitro* comprising the step of exposing the cells to a small organic molecule that interacts directly with at least one GAG in an amount sufficient for preventing the interactions of the GAG with at least one specific GBVP.

According to another embodiment the present invention provides a method for inhibiting virus attachment and entry *in vivo* comprising the step of administering a small organic molecule that interacts directly with at least one GAG in an amount sufficient for preventing the interactions of the GAG with at least one specific GBVP.

According to one embodiment, virus attachment and entry is inhibited by the interaction of the small compounds identified by the methods of the present invention with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives, and fragments thereof.

According to one currently preferred embodiment, virus attachment and entry is inhibited by the interaction of the small organic molecules identified by the methods of the present invention with HS-GAG or heparin or derivatives and oligosaccharide fragments thereof.

According to yet another embodiment, virus attachment and entry is inhibited by the interaction of the small organic molecule identified by the methods of the present invention with proteoglycan containing GAG, preferably HS-PG.

According to one embodiment, virus attachment and entry is inhibited by small compounds identified by the methods of the present invention that inhibit the interaction of GAGs with specific GBVPs selected from the group consisting of CMV envelope glycoprotein B, etc.

According to one currently preferred embodiment, the small compounds identified by the methods of the present invention inhibit the interaction of GAGs with CMV envelope glycoprotein B.

According to a further aspect the present invention provides a method for the treatment or prevention of disorders related to virus attachment and entry comprising the step of administering to a subject in need thereof a therapeutically effective amount of a small organic molecule identified by the methods of the present invention

that directly inhibits the interaction of GAGs with GAG specific GBVPs, preventing virus attachment and entry mediated by the GAG.

According to one embodiment, the small organic molecule for the treatment or prevention of a disorder related to virus attachment and entry is identified by the screening method comprising the steps of:

a. contacting a GAG with an GBVP in the presence of at least one candidate compound;

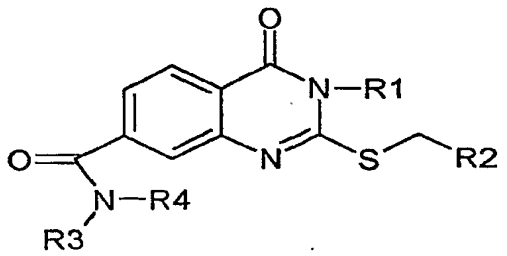
b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as an Inhibitor Compound, inhibiting GAG-GBVP interaction.

According to one embodiment, the disorder related to virus attachment and entry may be a CMV infection, HIV infection, etc.

According to one embodiment, the small organic molecules of the present invention are administered for treating or preventing a viral disorder, condition or process exemplified by, but not restricted to hepatitis B, HIV/AIDS, HSV-1, hepatitis C, HSV-2, HSV-7, CMV, RSV, Varicella Zoster Virus, Influenza Virus, Rhinovirus, Epstein-Barr Virus, Human Papilloma Virus and Dengue Virus.

According to yet another embodiment, the small organic molecules of the present invention are administered for treating or preventing of other infectious diseases which involve adhesion processes and cell entry, including, but not limited to, bacterial infection and malaria.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula I:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 and R_4 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is hydrogen and R_4 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_3 and R_4 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula I selected from:

2-[[(4-chlorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-methylphenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(3-fluorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[(2-oxo-2-phenylethyl)thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-oxo—4H-pyrido[1,2-a]pyrimidin-2-yl)methyl]thio]-3-(2-furanylmethyl)-3,4-dihydro-4-oxo-N-(2-methoxyethyl)-7-quinazolinecarboxamide

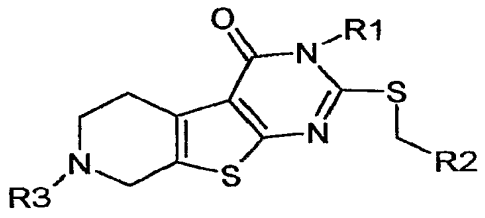
2-[(2-oxo-2-phenylethyl)thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(1-piperidinyl)propyl]-7-quinazolinecarboxamide

4-[[3,4-dihydro-4-oxo-3-pentyl-2-[(4-pyridinylmethyl)thio]-7-quinazolinyl]carbonyl]-1-piperazinecarboxylic acid ethyl ester

2-[[2-[[(3-chlorophenyl)methyl]thio]-3-pentyl-3,4-dihydro-4-oxo-N-(4-methylpiperazinyl)-7-quinazolinecarboxamide

2-[[2-oxo-2-(4-fluorophenyl)ethyl]thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula II:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 is selected from the group consisting of hydrogen; linear or branched chain C1-C6 loptionally substituted alkyl; arylalkyl, optionally substituted at the aryl group; cycloalkyl, optionally substituted with alkyl groups; alkanoyl; arylcarbonyl, optionally substituted at the aryl group; cycloalkylcarbonyl; alkoxycarbonyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is selelected from the group consisting of methyl, ethyl, 1-methylethyl, phenylmethyl,acetyl, eyhoxycarbonyl..

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula II selected from:

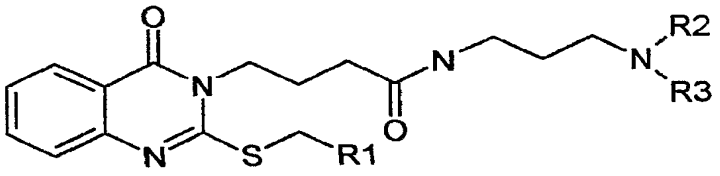
3-(4-ethoxyphenyl)-2-[[(4-fluorophenyl)methyl]thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one 3-phenyl-2-[(1-

naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(2-phenylethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-cyclohexyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(phenylmethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula III:



wherein:

R_1 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_2 and R_3 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_1 is selected from the group consisting of

4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_1 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_2 is hydrogen and R_3 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

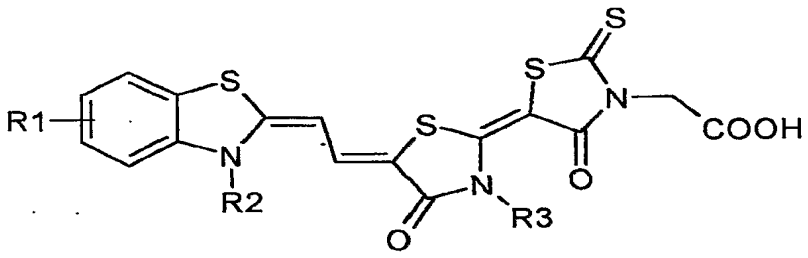
According to another embodiment, R_2 and R_3 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula III selected from:

2-[[(4-chlorophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide 2-[[(2-bromophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(1-naphthalenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula IV:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl,, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2 and R_3 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

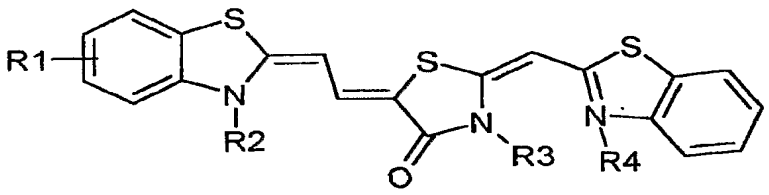
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IV selected from:

5-[3-ethyl-5-[(3-ethyl-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-ethyl-5-[(3-ethyl5,6-dimethoxy-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-(carboxymethyl) -5-[[5-cyano-3-(2-hydroxyethyl)-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula V:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl,

arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

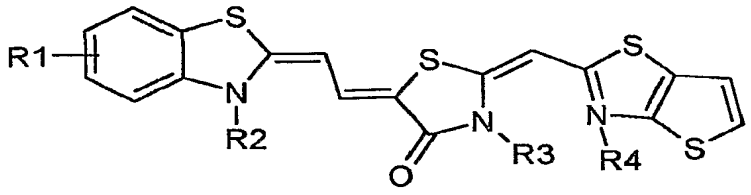
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula V selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] benzothiazolium (Compound No. 1313)

2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-3,6-dimethyl-benzothiazolium

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VI:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl,

arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

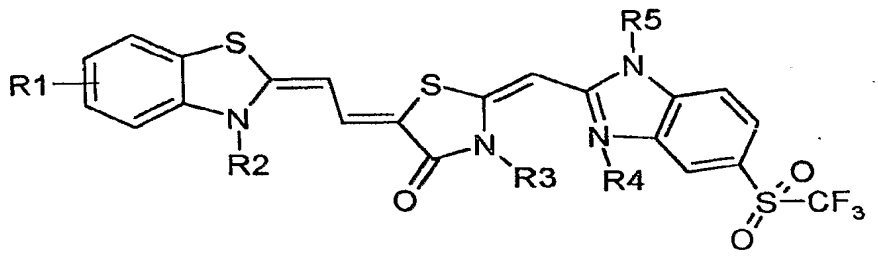
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VI selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium

3-(carboxymethyl)-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

R_5 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, aryl, optionally substituted on the aryl ring

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethyl

According to one embodiment R_5 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment R_5 is selected from the group consisting of phenyl, 4-methylphenyl, 3-methoxyphenyl

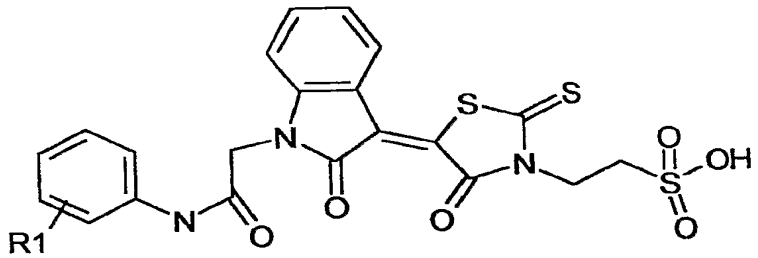
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VII selected from:

3-ethyl-2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-thiazolidinylidene]methyl] –1-phenyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-

thiazolidinylidene]methyl]-1,3-diethyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl.

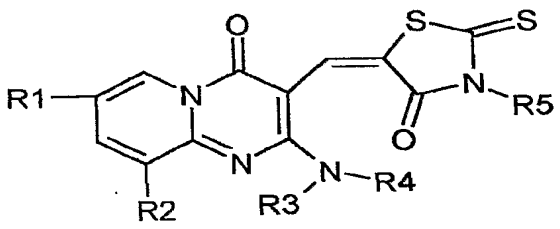
According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VIII selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid (Compound 11);

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

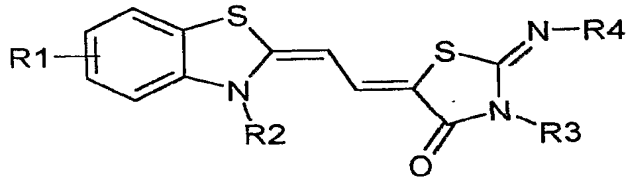
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylethyl)-4-oxo-2-thioxo-5-

thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No. 125).

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

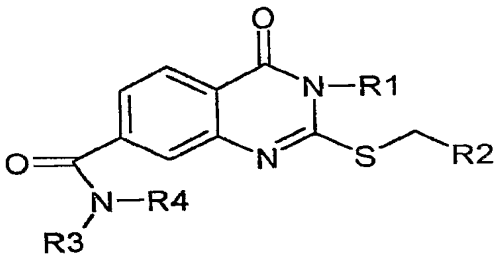
R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides compositions comprising the following compound of formula IX:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. **102**).

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a

subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula I:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 and R_4 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is hydrogen and R_4 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_3 and R_4 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula I selected from:

2-[[(4-chlorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-methylphenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(3-fluorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[(2-oxo-2-phenylethyl)thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-oxo—4H-pyrido[1,2-a]pyrimidin-2-yl)methyl]thio]-3-(2-furanylmethyl)-3,4-dihydro-4-oxo-N-(2-methoxyethyl)-7-quinazolinecarboxamide

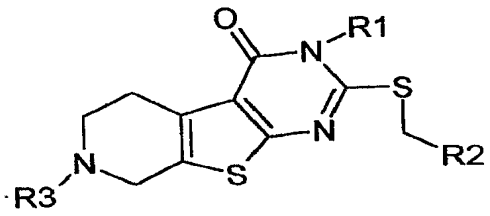
2-[(2-oxo-2-phenylethyl)thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(1-piperidinyl)propyl]-7-quinazolinecarboxamide

4-[[3,4-dihydro-4-oxo-3-pentyl-2-[(4-pyridinylmethyl)thio]-7-quinazolinyl]carbonyl]-1-piperazinecarboxylic acid ethyl ester

2-[[2-[[(3-chlorophenyl)methyl]thio]-3-pentyl-3,4-dihydro-4-oxo-N-(4-methylpiperazinyl)-7-quinazolinecarboxamide

2-[[2-oxo-2-(4-fluorophenyl)ethyl]thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula II:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 is selected from the group consisting of hydrogen; linear or branched chain C1-C6 loptionally substituted alkyl; arylalkyl, optionally substituted at the aryl group; cycloalkyl, optionally substituted with alkyl groups; alkanoyl; arylcarbonyl, optionally substituted at the aryl group; cycloalkylcarbonyl; alkoxycarbonyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of

phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is selelected from the group consisting of methyl, ethyl, 1-methylethyl, phenylmethyl,acetyl, eyhoxycarbonyl..

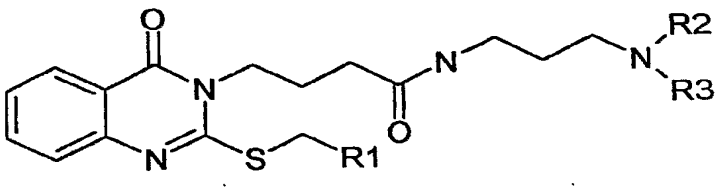
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula II selected from:

3-(4-ethoxyphenyl)-2-[[(4-fluorophenyl)methyl]thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one 3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(2-phenylethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-cyclohexyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(phenylmethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula III:



wherein:

R_1 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_2 and R_3 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_1 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_1 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_2 is hydrogen and R_3 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_2 and R_3 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

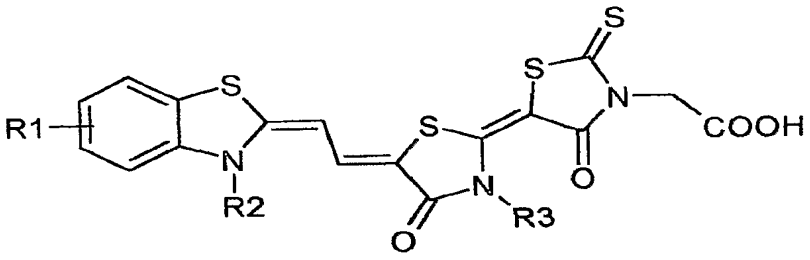
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula III selected from:

2-[[(4-chlorophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide 2-[[(2-bromophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(1-naphthalenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated

by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IV:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl,, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2 and R_3 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IV selected from:

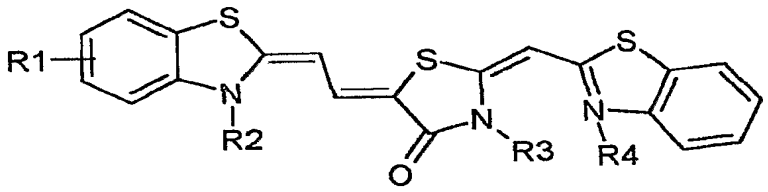
5-[3-ethyl-5-[(3-ethyl-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-

thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-ethyl-5-[(3-ethyl5,6-dimethoxy-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-(carboxymethyl) -5-[[5-cyano-3-(2-hydroxyethyl)-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula V:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

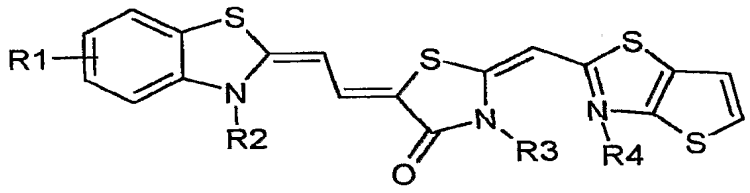
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula V selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] benzothiazolium (Compound No. **1313**)

2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-3,6-dimethyl-benzothiazolium

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VI:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

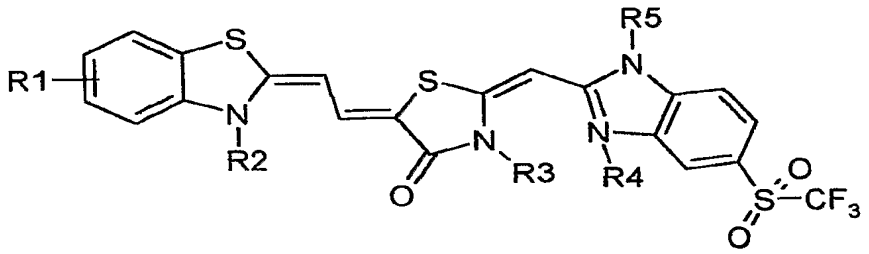
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VI selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium

3-(carboxymethyl)-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

R_5 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, aryl, optionally substituted on the aryl ring

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethyl

According to one embodiment R_5 is selected from the group consisting of methyl, ethyl, hydroxyethyl

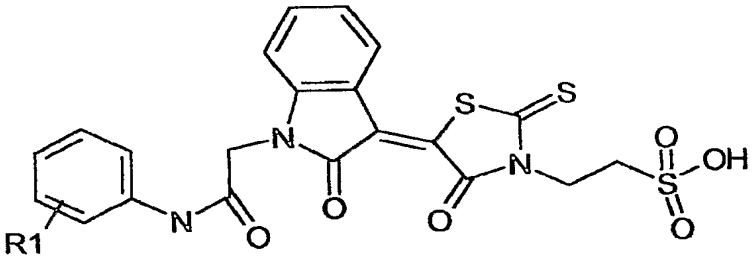
According to another embodiment R_5 is selected from the group consisting of phenyl, 4-methylphenyl, 3-methoxyphenyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VII selected from:

3-ethyl-2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-thiazolidinylidene]methyl] –1-phenyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-1,3-diethyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl.

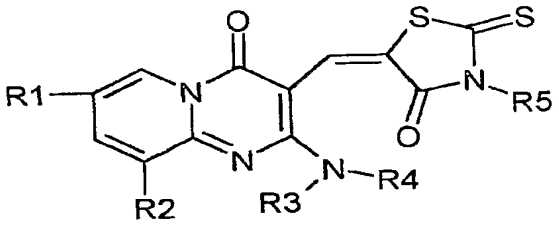
According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VIII selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid (Compound 11);

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

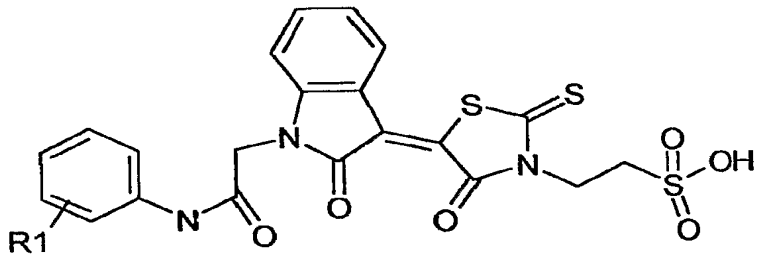
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No. 125).

According to another aspect, the present invention provides a method for the

treatment or prevention of Varicella Zoster Virus infection, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl.

According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl.

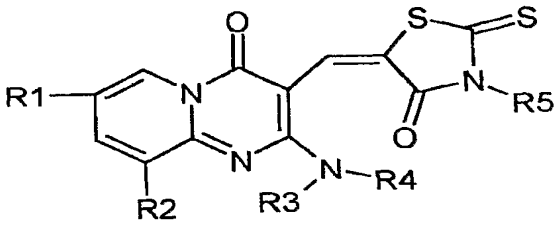
According to another embodiment the compound of formula VIII is selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid (Compound 11);

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to another aspect, the present invention provides a method for the treatment or prevention of hepatitis C infection, comprising the step of administering

to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

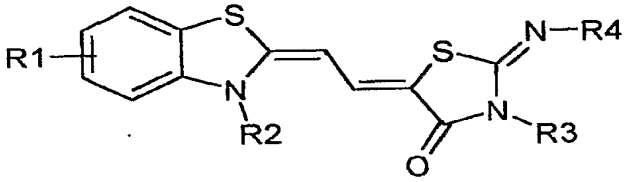
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No.

125).

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

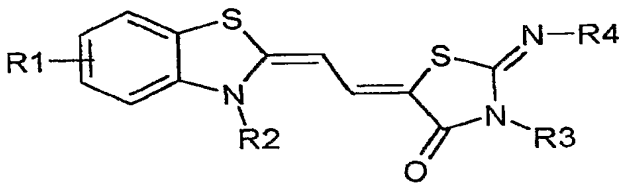
R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides a method of teatment with the following compound of formula X:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. **102**).

According to another aspect, the present invention provides a method for the treatment or prevention of hepatitis C infection, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides a method of treatment hepatitis C with the following compound of formula X:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. 102).

Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows CMV glycoprotein B binding to immobilized heparin

FIG. 2 demonstrates inhibition of CMV glycoprotein B binding to immobilized heparin by soluble heparin.

DETAILED DESCRIPTION OF THE INVENTION

It is an object of the present invention to provide methods for screening and identifying compounds capable of inhibiting interaction between glycosaminoglycans (GAGs) and specific GAG-Binding Viral Proteins (GBVPs).

It is another object of the present invention to provide methods for screening and identifying compounds capable of direct inhibition of GAG-mediated virus attachment and entry into cells.

It is another object of some aspects of the present invention to provide pharmaceutical compositions comprising small organic compounds for medical and diagnostic use, wherein the small organic compounds are inhibitors of the interactions between GAGs and viruses and more specifically between heparan sulfate and specific GBVPs. Accordingly, these compositions are useful as inhibitors of virus attachment and entry. In addition, the compositions interact directly with HS-GAGs and are therefore useful as inhibitors of any HS-GAG mediated processes and conditions.

It is yet another object of the present invention to provide methods for the treatment of diseases or disorders associated with virus attachment and entry into cells mediated by the interactions between GAGs and specific GBVPs.

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "compound" refers to small organic molecule having a molecular weight less than 1500 Daltons and preferably between 300 to 1200 Daltons.

The term "HS-GAG" refers to heparan sulfate glycosaminoglycan. It includes fragments of heparan sulfate such as those that may be produced chemically, enzymatically or during purification. It includes the HS-GAG chains of proteoglycans such as heparan sulfate proteoglycans. HS-GAG may be free or attached to a linker, support, cell or protein, or otherwise chemically or enzymatically modified. HS-GAGs may be crude or purified from organs, tissues or cells.

The term "GAG" refers to glycosaminoglycans, including heparan sulfate (that is referred to in the art also as HS-GAG), heparin, chondroitin sulfate, dermatan sulfate and keratan sulfate. It includes the GAG chains of proteoglycans such as heparan sulfate proteoglycan or chondroitin sulfate proteoglycan.

"HS-PG" or "HSPG" refers to heparan sulfate proteoglycans.

"Heparin" is polysulfated polysaccharide, with no protein associated with it. As used herein, heparin refers to heparin prepared from different organs or species such as porcine intestinal mucosa heparin. It includes low molecular weight heparins, such as commercially available Fraxiparin, and other heparin derivatives, prepared or modified by chemical or enzymatic reaction.

"Heparin Derivatives" consist of products derived from heparin, made by one or more chemical or enzymatic modifications. The modifications are designed to change the activity of relevant groups of the molecules.

"Heparin Derived Oligosaccharides" are products made from heparin by controlled cleavage and subsequent purification.

"Heparan Derivatives" consist of products derived from heparan sulfate, made by one or more chemical or enzymatic modifications. The modifications are designed to change the activity of relevant groups of the molecules.

"Heparan Derived Oligosaccharides" are products made from heparan sulfate by controlled cleavage and subsequent purification.

The term "specific GBVP" means a specific viral protein adhesion molecule and refers to a GAG-binding protein molecule involved in mediating virus attachment and virus-cell interaction and having a heparin-binding domain. Example is CMV envelope glycoprotein B and the like. It includes mutant proteins, protein domains, peptide fragments and the like, that retain the GAG binding domain (heparin-binding domain).

The term "Inhibitor Compound" refers to a small organic molecule inhibiting the interaction (binding) between two molecules: (1) a GAG, exemplified by, but not restricted to heparin or HS-GAG and (2) an GBVP, exemplified by, but not restricted to CMV envelope glycoprotein B.

The term "synthetic chemical compound collection" or "compound collection" refers to a collection of random and semi-random synthetic molecules wherein each member of such collection or library is produced by chemical or enzymatic synthesis.

The term "treatment" or "treating" is intended to include the administration of

the compound of the invention to a subject for purposes which may include prophylaxis, amelioration, prevention or cure of disorders mediated by virus attachment and infection events. Such treatment need not necessarily completely ameliorate the viral infection or other responses related to the specific disorder. Further, such treatment may be used in conjunction with other traditional treatments for reducing the disease or disorder condition known to those of skill in the art.

The methods of the invention may be provided as a "preventive" treatment before detection of, for example, a viral infection, so as to prevent the disorder from developing in patients at high risk for the same, such as, for example, transplant patients.

As used through this specification and the appended claims, the singular forms "a", "an" and "the" include the plural unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes mixtures of such compounds, reference to "a P-selectin", or "an L-selectin" includes reference to respective mixtures of such molecules, reference to "the formulation" or "the method" includes one or more formulations, methods and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure.

Methods for compound screening and drug discovery

Currently, attempts at modulating GAG interactions with GAG specific GBVPs are indirect, targeting the heparin-binding domains associated with specific GBVPs by using GAG-mimetics such as heparins, derivatives and other sulfated GAG mimetics.

The present invention provides a method for screening and identifying compounds for drug development, disclosing GAGs, specifically HS-GAGs as novel molecular targets for such screening. The direct targeting of GAGs as described herein is of critical importance, since modern drug discovery requires precise knowledge of the molecular nature of the drug binding site for efficient drug screening and chemical optimization.

According to one aspect, the present invention provides a method of screening for small compounds that directly inhibit the interaction of GAGs with specific GBVPs, the method comprising the steps of:

a. contacting a GAG with a GBVP in the presence of at least one candidate

compound;

b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as an Inhibitor Compound, inhibiting GAG-GBVP interaction.

The compound screening methods for identification of Inhibitor Compounds may be used in various modifications, which are well known to one skilled in the art. Assays can be classified as either direct binding assays or inhibition assays. The GAG molecule may be immobilized, or GBVP may be immobilized or both GAG and GBVP may be present in solution. Detection may focus either on GAG or on GBVP, for instance by using antibodies, biotin-streptavidin, radiolabeling, fluorescent label, etc. Detection methods may also differ, such as spectrophotometry, chemoluminiscence, fluorescence, radioactive detection, etc. Immobilized GAGs may be used coated on plates or coupled to beads. GAGs may be linked to a carrier such as a protein, using different chemical methods. Alternatively, the GBVPs may be immobilized, for instance by coating plates or coupling to beads. GBVPs may be used as fusion proteins or domains containing the GAG-binding domain. Another useful approach may be to use as a source of GAG a whole cell such as a fibroblast cell. This is particularly relevant for identifying Inhibitor Compounds that prevent adhesion to such fibroblast cells.

According to one embodiment, compounds for screening may be produced by synthetic chemistry or may be natural compounds, individual or in mixtures, pre-selected by an algorithm, compressed libraries and the like. A preferred method of screening is known as High-Throughput Screening (HTS), in which thousands of compounds are screened with the aid of robotics.

According to one currently preferred embodiment compound screening according to the method of the present invention is used as iterative screening in conjunction with chemical optimization via synthetic chemistry.

According to one embodiment, the small organic molecules screened by the methods of the present invention interact with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate, and derivatives and fragments thereof.

According to one currently preferred embodiment, the glycosaminoglycans are

HS-GAG or heparin or derivatives and oligosaccharide fragments thereof. GAGs may be crude or purified from an organ, tissue or cell. Such HS-GAGs may be commercially available, or purified from source of interest such as human liver, human brain, endothelial cells and the like. The HS-GAGs may be also chemically or enzymatically modified, or produced synthetically.

According to another embodiment the small compounds screened by the methods of the present invention interact with proteoglycan containing GAG, particularly heparan sulfate proteoglycan (HS-PG). Proteoglycans having HS-GAG chains may be purified from an organ, tissue, cell or tumor. Examples for such HS-PGs are syndecan or aggrin. Proteoglycans having other GAG chains, such as versican, may be also used.

According to one embodiment, the small organic molecules screened by the methods of the present invention inhibit the interaction of GAGs with specific GBVPs selected from the group consisting of CMV envelope glycoprotein B, etc.

According to one currently preferred embodiment, the small compounds screened by the methods of the present invention inhibit the interaction of GAGs with CMV envelope glycoprotein B, namely the interaction of the GAG with the heparin binding domain of CMV envelope glycoprotein B.

Assays for CMV envelope glycoprotein B binding to heparin have been previously described; however, the present invention discloses for the first time the use of CMV envelope glycoprotein B for compound screening and for direct targeting of GAG binding sites. The screening method of the present invention is based on an ELISA assay for CMV envelope glycoprotein B interaction with heparin on 96-well plates, suitable for screening compound collections, newly developed by the inventors of the present invention. The assay measures binding of CMV envelope glycoprotein B to immobilized heparin. The amount of bound CMV envelope glycoprotein B is determined by an ELISA assay using a monoclonal antibody conjugated to horseradish peroxidase. Fig. 1 shows CMV envelope glycoprotein B binding to heparin. As expected, soluble heparin inhibited CMV envelope glycoprotein B binding to immobilized heparin (Fig. 2). This method can be used with other specific GBVPs such as hepatitis C envelope glycoprotein, etc. Additionally, other GAGs are capable of replacing heparin in this kind of assay. In particular, in place of heparin one may immobilize a different HS-GAG such as purified HS-GAG from an organ, tissue or cell of interest. HS-GAGs may be immobilized by methods similar for

immobilization of heparin, or by other means known in the art.

Preferably, when using this kind of assay for compound screening, one may use a particular GAG or PG from a target tissue, such as endothelial cell HS-GAG, kidney purified HS-GAG or HS-PG, and the like. The reason is that molecular diversity of HS-GAGs is regulated in a tissue and cell-specific manner and different HS-GAGs have different binding sites for GAG specific GBVPs.

The present invention demonstrates for the first time that this kind of GAG-viral protein interaction assay is suitable for screening collections of compounds and for discovery of novel drugs. As described herein below, the CMV envelope glycoprotein B assay was used to screen a collection of several thousand compounds on 96-well plates. For this purpose, the compounds in individual wells were co-incubated with CMV envelope glycoprotein B on plates containing immobilized heparin. Following completion of assay and color development, percentage of inhibition obtained for each compound was determined. Positive and negative controls were included on every plate. Compounds that inhibited at least 30% of the signal were scored as hits and selected for further analysis. Examples of Inhibitor Compounds are given in Example 4, Table 1.

According to one embodiment of the present invention, the inhibitor compounds identified by the methods of the present invention directly interact with GAGs and inhibit their interaction with specific GBVPs.

In principle, the inhibitor compounds can inhibit CMV envelope glycoprotein B -heparin interaction either (i) by direct binding to heparin and thus preventing its interaction with CMV envelope glycoprotein B or (ii) by direct binding to CMV envelope glycoprotein B and subsequently preventing its interaction with heparin (a third theoretical possibility is that the compound binds to both heparin and CMV envelope glycoprotein B, but this is statistically a very rare possibility).

Compounds found to be suitable for further development and chemical optimization may be further subjected to a second screening, identifying those that directly bind to heparin. Individual compounds are incubated with immobilized heparin in the absence of CMV envelope glycoprotein B. After washing of the plates to remove all unbound compound, CMV envelope glycoprotein B is added. At this time, in separate wells, CMV envelope glycoprotein B is co-incubated with the test compounds and the standard assay protocol is followed. Test compounds which bind directly and irreversibly to heparin are identified by comparing the results of pre-

incubation versus co-incubation experiments.

As exemplified for the first time by the present invention, structurally diverse compounds are capable of inhibiting GAG interactions with GBVPs. Such inhibitor compounds may have therapeutic implications and may be useful for a variety of disorders, since GAGs and GBVPs have many biological roles and have been implicated in a multitude of disorders.

Methods for modulating virus attachment and entry into cells

According to another aspect the present invention provides methods for modulation of virus attachment and entry *in vivo* or *in vitro* mediated by interactions of GAGs and GAG specific GBVPs.

According to one embodiment the present invention provides a method for inhibiting virus attachment and entry *in vitro* comprising the step of exposing the cells to a small organic molecule that interacts directly with at least one GAG in an amount sufficient for preventing the interactions of the GAG with at least one specific GBVP.

According to another embodiment the present invention provides a method for inhibiting virus attachment and entry *in vivo* comprising the step of administering a small organic molecule that interacts directly with at least one GAG in an amount sufficient for preventing the interactions of the GAG with at least one GBVP.

According to one embodiment, virus attachment and entry is inhibited by the interaction of the small compounds identified by the methods of the present invention with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

According to one currently preferred embodiment, virus attachment and entry is inhibited by the interaction of the small organic molecules identified by the methods of the present invention with HS-GAG or heparin.

According to yet another embodiment, virus attachment and entry is inhibited by the interaction of the small organic molecule identified by the methods of the present invention with proteoglycan containing GAG, preferably HS-PG.

According to one embodiment, virus attachment and entry is inhibited by compounds identified by the methods of the present invention that inhibit the interaction of GAGs with GAG specific GBVPs selected from the group consisting of CMV envelope glycoprotein B, etc.

According to one currently preferred embodiment, the small compounds identified by the methods of the present invention inhibit the interaction of GAGs with CMV envelope glycoprotein B.

Methods for treatment of disorders related to virus attachment and entry into cells

According to yet another aspect the present invention provides a method for the treatment or prevention of disorders related to virus attachment and entry comprising the step of administering to a subject in need thereof a therapeutically effective amount of a small organic molecule identified by the methods of the present invention that directly inhibits the interaction of GAGs with a GBVPs, preventing virus attachment and entry mediated by the GAG.

Blocking virus attachment and entry has proven to be highly effective in the treatment of number of viral diseases and disorders including HIV, etc..

According to one embodiment, the small organic molecule for the treatment or prevention of a disorder related to virus attachment and entry is identified by the screening method comprising the steps of:

a. contacting a GAG with an GBVP in the presence of at least one candidate compound;

b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as an Inhibitor Compound, inhibiting GAG-GBVP interaction.

According to another embodiment the GAGs of the inhibited GAG-GBVP interactions are selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate, and derivatives and fragments thereof.

According to one currently preferred embodiment, the GAGs of the inhibited GAG-GBVP interactions are selected from the group consisting of HS-GAG and heparin.

According to yet another embodiment the GBVPs of the inhibited GAG-GBVP interactions are selected from the group consisting of CMV envelope glycoprotein B, etc.

According to one currently preferred embodiment, the GBVPs of the inhibited GAG-GBVP interactions are selected from the group consisting of CMV envelope glycoprotein B.

Virus attachment is the first event in the pathological cascade of the invection. Viral envelope proteins, those which contact and mediate fusion with viral host cells, are therefore potential targets for anti-viral therapies (Faulkner L et al 2003, Vaccine 21:932-9)

The present invention discloses methods of screening for small organic molecules capable of inhibiting GAG interaction with GBVPs; the present invention further shows that such Inhibitor Compounds are useful as inhibitors of virus-cell adhesion processes and, moreover, are useful for the prevention or treatment of diseases associated with virus attachment, entry and infection.

According to one embodiment, the small organic molecules of the present invention are administered for treating or preventing a viral disorder, condition or process exemplified by, but not restricted to AIDS, CMV, RSV, HSV, VZV.

According to one embodiment, the inhibitor compounds inhibit virus attachment, entry or infection.

Human Herpes Viruses (HHVs) are human pathogens which cause a variety of disease states including cold sores, eye and genital infections, life-threatening neonatal infections, and encephalitis. Cell surface heparan sulfate (HS) serves as an initial attachment receptor for several HHVs (Akula SM etal 2001, Virol. 284:235-49). The gamma 2-human herpes-8 (HHV-8) or Kaposi's sarcoma associated herpes virus infects a variety of human and animal cell lines. Studies showed that this broad cellular tropism may in part be due to HAV-8's interaction with the ubiquitous host cell-surface GAG, HS. The HHV-8 envelope glycoprotein B (HHV-8gB) possesses a putative heparin-binding domain which specifically bound heparan in vitro. This data, combined with in vivo results showing that HHV-8 attachment and infection was inhibited by soluble HS, strongly suggests that HHV-8gB plays an important role in the infectious process.

To investigate the role of cell surface GAGs, including heparan sulfate (HS-GAG), on HIV-1 infection in human T cells, HIV-1 binding and infection were determined after treatment of T-cell lines and CD4+ T cells from normal peripheral blood mononuclear cells (PBMC) with GAG-degrading enzyme or a GAG metabolic sulfation inhibitor. Heparitinase I (hep I) prevented binding of HIV-1/IIIB to MT-4

cells as revealed by indirect immunofluorescence procedures, thereby inhibiting infection. Hep I was less effective in the binding inhibition of the macrophage-tropic strain HIV-1/SF162 than that of the T-cell line-tropic strain HIV-1/IIIB. The binding of HIV-1/SF162 was about 100-fold less dependent on cell surface HS-GAG than HIV-1/IIIB. Human HTLV-I positive T-cell lines expressed more HS-GAG than HTLV-I negative T-cell lines or normal CD4+ T cells when stained with anti-HS-GAG mAbs against either native or heparitinase-treated HS-GAG. With the exception of endo-beta-galactosidase (endo-beta-gal), GAG-degrading enzymes, including hep I, chondroitinase ABC (chon ABC), chondroitinase AC II (chon AC II) and keratanase, did not prevent the binding of HIV-1/IIIB to CD4+ T cells from normal PBMC. These results indicate that the cell surface HS-GAG of human T cells participates in HIV-1 infection by facilitating HIV-1/IIIB binding to MT-4 cells. In particular, the sulfation of HS-GAG chains is critical. Since the expression of cell surface HS-GAG varies among T cells, which are not consistently sensitive to hep I treatment in HIV-1 binding inhibition, other GAG-like molecules may also be involved.

Dengue virus is a human pathogen that has reemerged as an increasingly important public health threat. The cellular receptor utilized by dengue envelope protein to bind to target cells is a highly sulfated type of heparan sulfate (Marks RM et al 2001, J Med.Chem. 44:2178-87). Heparin, highly sulfated heparan sulfate, and the polysulfonate pharmaceutical Suramin effectively prevented dengue virus infection of target cells, indicating that the envelope protein-target cell receptor interaction is a critical determinant of infectivity. The dengue envelope protein sequence includes two putative GAG-binding motifs at the carboxy terminus; the first could be structurally modeled and formed an unusual extended binding surface of basic amino acids. Similar motifs were also identified in the envelope proteins of other flaviviridae. Developing pharmaceuticals that inhibit target cell binding may be an effective strategy for treating flavivirus infections.

The Cytomegaloviruses (CMVs) are a distinct, widely distributed sub-group of herpes viruses. In most areas of the world, human CMV spreads at an early age and affects a large majority of the population. The importance of CMV as a pathogen has arisen with the increase in organ allografting and immunosuppressive post-transplant therapies and the increase in acquired immunodeficiency syndrome (AIDS). These conditions predispose individuals to a primary CMV infection or to reactivation of

latent infection, which may lead to fulminent, life threatening disease (Drew WL et al 1999, Curr.Clin.Top. Infect. Dis. 19:16-29). The virion carries two prominent herpes-virus-conserved glycoprotein complexes. One is composed of covalently linked, proteolytically processed, dimers of glycoprotienB (gB), which plays a critical role in viral entry. gB is the major HS proteoglycan-binding glycoprotein (Compton T 1993, Virol 193:84-841). The heparin binding properties of a synthetic peptide deduced from the sequence of human CMV gB were investigated (Silvestri ME and Sundquist VA 2001, Scan. J Immunol. 53:282-9). The peptide bound heparin in vitro and bound to human cells in a manner suggesting an interaction with extracellular matrix. Binding of the peptide to human fibroblasts could be inhibited both by adding soluble heparin and by enzymatic pretreatment of the cells with heparinase. This evidence supports the claim that CMV gB binding to cell surface HS is a critical step in viral attachment and infection.

According to another embodiment, the small organic molecules of the present invention are administered for treating or preventing malaria. Severe Plasmodium falciparum malaria is characterized by excessive sequestration of infected and uninfected erythrocytes in the microvasculature of the infected organ. Roseting, the adhesion of P.falciparum-infected erthrocytes to uninfected erthroctyes is a virulent parasite phenotype associated with the occurrence of severe malaria. The adhesion ligand, P.falciparum erthrocyte membrane protein 1 (PfEMP1) contains clusters of GAG-binding motifs (Chen Q et al 1998, J Exp. Med. 187:15-23). The adhesive interactions could be inhibited with HS or heparitinases. P.falciparum is another example of an infectious agent which has evolved a molecular mechanism to exploit cell surface GAGs to facilitate or effect cell entry.

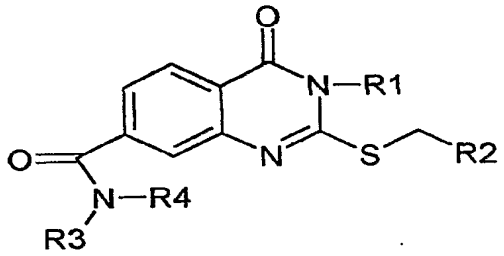
According to another embodiment, the small organic molecules of the present invention are administered for treating or preventing bacterial infections. Present in the extracellular matrix and membranes of virtually all animal cells, GAGs are among the first host macromolecules encountered by infectious agents. Pathogenic bacteria exploit the GAGs to attach to target cells using bacterially expressed "adhesins" (Menozzi FD et al 2002, Mol.Microbiol. 43:1379-86). Some pathogens, such as Bordetella pertussis and Chlamydia trachomatis, may express more than one GAG-binding adhesins. Bacterial interactions with PGs may also facilitate cell invasion or system dissemination, as observed for Neisseria gonorrhoeae and Mycobacterium tuberculosis respectively. A specific example of enhanced bacterial virulence through

exploitation of host GAGs is the Lyme disease spirochaete (Parveen N et al 2003, Mol.Microbiol. 47:1433-44). The Lyme disease spirochaete, Borrelia burgdorferi, is transmitted to mammals by Ixodes ticks and can infect multiple tissues. Host cell attachment may be critical for tissue colonization and B. burgdorferi cultivated in vitro recognizes heparin and deramatan sulfate-related GAGs on the surface of mammalian cells. Host-adapted B. burgdorferi exhibited approximately three fold better binding to purified GAGs and those expressed on the surface of cultured endothelial cells. Three B. burgdorferi surface proteins, Bgp, DbpA and DbpB bind to GAGs and were shown to be present on the bacterial surface at higher levels after host adaptation.

Pharmaceutical Compositions

Here we describe pharmaceutical compositions comprising compounds that were identified as Inhibitor Compounds. Certain compounds were discovered in drug screening described in Example 4 and Table 1. Other compounds were discovered as Inhibitor Compounds directly interacting with GAGs, see Example 7 and Table 2. Some other Inhibitor Compounds were discovered to inhibit virus infectivity in cell culture systems, see Examples 8-10.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula I:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 and R_4 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is hydrogen and R_4 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_3 and R_4 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula I selected from:

2-[[(4-chlorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-methylphenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(3-fluorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[(2-oxo-2-phenylethyl)thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-oxo—4H-pyrido[1,2-a]pyrimidin-2-yl)methyl]thio]-3-(2-furanylmethyl)-3,4-dihydro-4-oxo-N-(2-methoxyethyl)-7-quinazolinecarboxamide

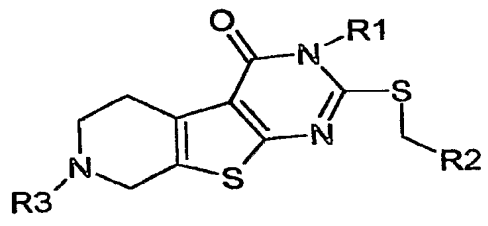
2-[(2-oxo-2-phenylethyl)thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(1-piperidinyl)propyl]-7-quinazolinecarboxamide

4-[[3,4-dihydro-4-oxo-3-pentyl-2-[(4-pyridinylmethyl)thio]-7-quinazolinyl]carbonyl]-1-piperazinecarboxylic acid ethyl ester

2-[[2-[[(3-chlorophenyl)methyl]thio]-3-pentyl-3,4-dihydro-4-oxo-N-(4-methylpiperazinyl)-7-quinazolinecarboxamide

2-[[2-oxo-2-(4-fluorophenyl)ethyl]thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula II:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 is selected from the group consisting of hydrogen; linear or branched chain C1-C6 loptionally substituted alkyl; arylalkyl, optionally substituted at the aryl group; cycloalkyl, optionally substituted with alkyl groups; alkanoyl; arylcarbonyl, optionally substituted at the aryl group; cycloalkylcarbonyl; alkoxycarbonyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is selelected from the group consisting of methyl, ethyl, 1-methylethyl, phenylmethyl,acetyl, eyhoxycarbonyl..

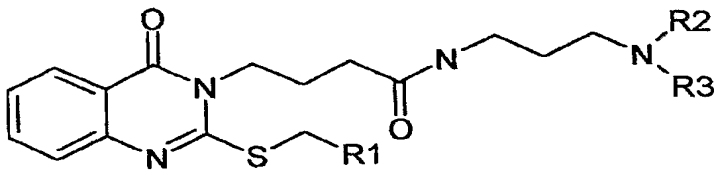
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula II selected from:

3-(4-ethoxyphenyl)-2-[[(4-fluorophenyl)methyl]thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one 3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(2-phenylethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-cyclohexyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(phenylmethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula III:



wherein:

R_1 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_2 and R_3 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_1 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_1 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_2 is hydrogen and R_3 is selected from the group

consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

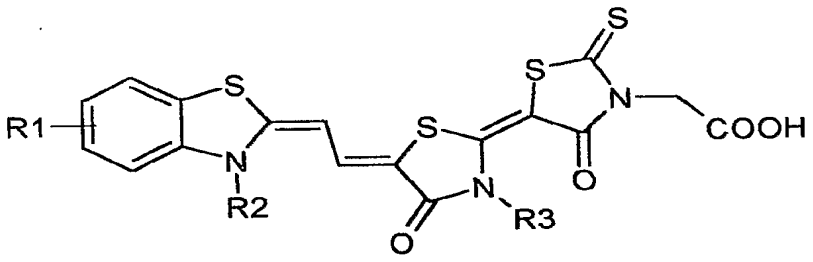
According to another embodiment, R_2 and R_3 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula III selected from:

2-[[(4-chlorophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide 2-[[(2-bromophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(1-naphthalenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula IV:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl,, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2 and R_3 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

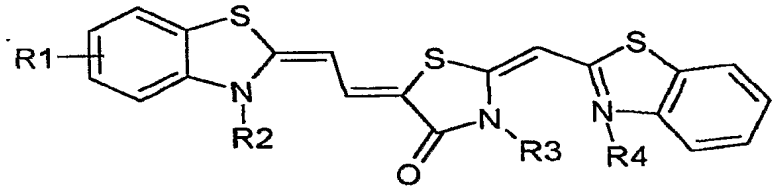
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IV selected from:

5-[3-ethyl-5-[(3-ethyl-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-ethyl-5-[(3-ethyl5,6-dimethoxy-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-(carboxymethyl) -5-[[5-cyano-3-(2-hydroxyethyl)-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula V:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

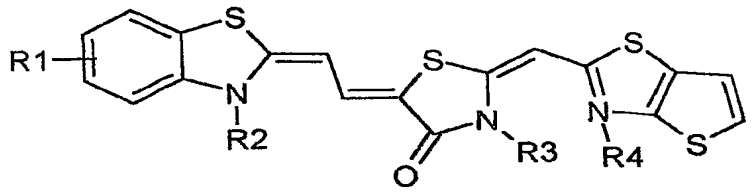
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula V selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] benzothiazolium (Compound No. 1313)

2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-3,6-dimethyl-benzothiazolium

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VI:



:

wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

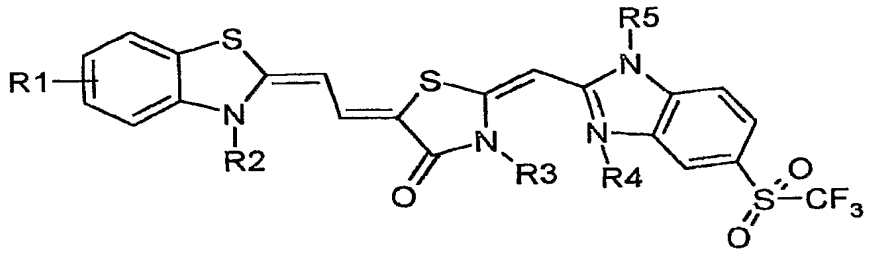
According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VI selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium

3-(carboxymethyl)-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

R_5 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, aryl, optionally substituted on the aryl ring

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethyl

According to one embodiment R_5 is selected from the group consisting of methyl, ethyl, hydroxyethyl

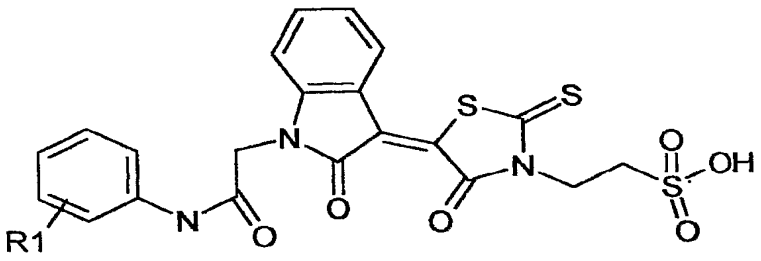
According to another embodiment R_5 is selected from the group consisting of phenyl, 4-methylphenyl, 3-methoxyphenyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VII selected from:

3-ethyl-2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-thiazolidinylidene]methyl] –1-phenyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-1,3-diethyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium.

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl.

According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl.

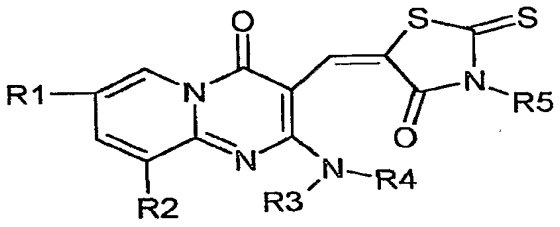
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VIII selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid (Compound 11);

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to one aspect, the present invention provides a pharmaceutical

composition comprising as an active ingredient a compound of the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

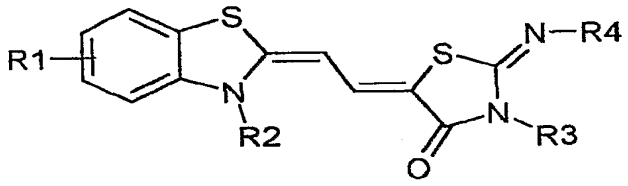
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-

thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No. 125).

According to one aspect, the present invention provides a pharmaceutical composition comprising as an active ingredient a compound of the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

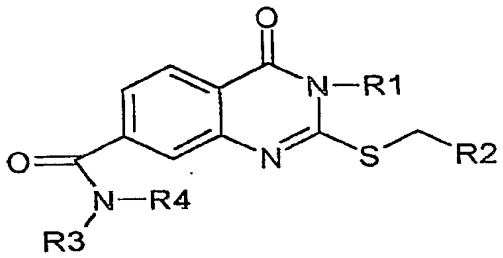
R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides compositions comprising the following compound of formula IX:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. 102).

Methods of treatment of viral disorders

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula I:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 and R_4 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is hydrogen and R_4 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_3 and R_4 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula I selected from:

2-[[(4-chlorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-methylphenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(3-fluorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[(2-oxo-2-phenylethyl)thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-oxo—4H-pyrido[1,2-a]pyrimidin-2-yl)methyl]thio]-3-(2-furanylmethyl)-3,4-dihydro-4-oxo-N-(2-methoxyethyl)-7-quinazolinecarboxamide

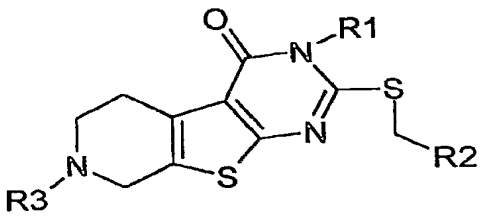
2-[(2-oxo-2-phenylethyl)thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(1-piperidinyl)propyl]-7-quinazolinecarboxamide

4-[[3,4-dihydro-4-oxo-3-pentyl-2-[(4-pyridinylmethyl)thio]-7-quinazolinyl]carbonyl]-1-piperazinecarboxylic acid ethyl ester

2-[[2-[[(3-chlorophenyl)methyl]thio]-3-pentyl-3,4-dihydro-4-oxo-N-(4-methylpiperazinyl)-7-quinazolinecarboxamide

2-[[2-oxo-2-(4-fluorophenyl)ethyl]thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula II:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 is selected from the group consisting of hydrogen; linear or branched chain C1-C6 loptionally substituted alkyl; arylalkyl, optionally substituted at the aryl group; cycloalkyl, optionally substituted with alkyl groups; alkanoyl; arylcarbonyl, optionally substituted at the aryl group; cycloalkylcarbonyl; alkoxycarbonyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of pentyl, phenyl, 4-fluorophenyl.

According to another embodiment, R_1 is 2-furanylmethyl or (tetrahydro-2-furanyl)methyl.

According to one embodiment, R_2 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_2 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_2 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_3 is seleelected from the group consisting of methyl, ethyl, 1-methylethyl, phenylmethyl,acetyl, eyhoxycarbonyl..

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula II selected from:

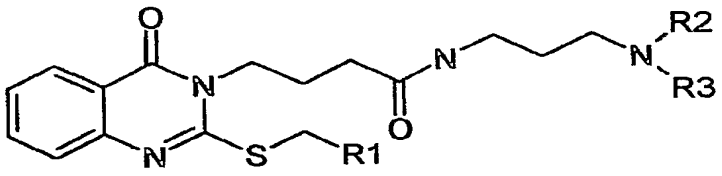
3-(4-ethoxyphenyl)-2-[[(4-fluorophenyl)methyl]thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(2-phenylethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

3-cyclohexyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(phenylmethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula III:



wherein:

R_1 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_2 and R_3 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-

7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of phenyl, 4-methylphenyl, 3(4)-fluoro- or 3(4)-chlorophenyl, naphthalene.

According to another embodiment, R_1 is selected from the group consisting of 4-pyridinyl or 4-oxo-4H-pyrido[1,2-a]pyrimidin-yl.

According to yet another embodiment, R_1 is selected from the group consisting of phenylcarbonyl and 4-fluoro(or chloro)phenylcarbonyl.

According to one embodiment, R_2 is hydrogen and R_3 is selected from the group consisting of 3-(4-morpholinyl)propyl, 3-(1-piperidinyl)propyl, 2-methoxyethyl

According to another embodiment, R_2 and R_3 form 4-methylpiperazinyl or 1-piperazinyl-4-carboxylic acid ethyl ester.

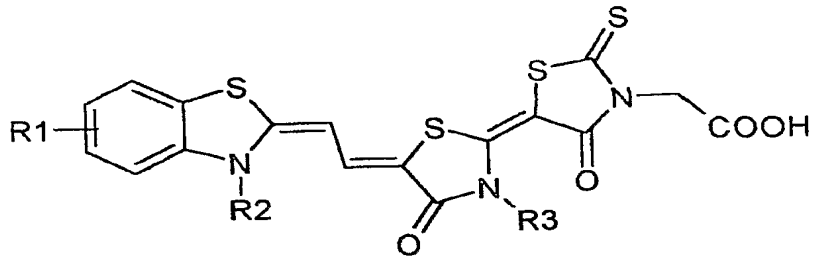
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula III selected from:

2-[[(4-chlorophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide (K284-4381)

2-[[(2-bromophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(1-naphthalenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IV:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl,, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2 and R_3 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IV selected from:

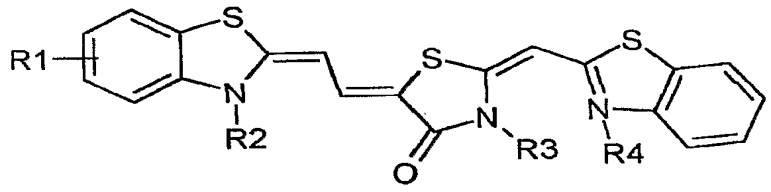
5-[3-ethyl-5-[(3-ethyl-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-ethyl-5-[(3-ethyl5,6-dimethoxy-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-(carboxymethyl) -5-[[5-cyano-3-(2-hydroxyethyl)-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-

thiazolidineacetic acid.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula V:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl

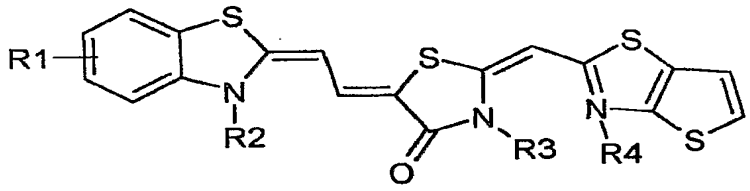
According to certain preferred embodiment the present invention provides compositions comprising compounds of formula V selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-

thiazolidinylidene]methyl] benzothiazolium (Compound No. 1313)

2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-3,6-dimethyl-benzothiazolium.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VI:



:

wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethy, carboxymethyl.

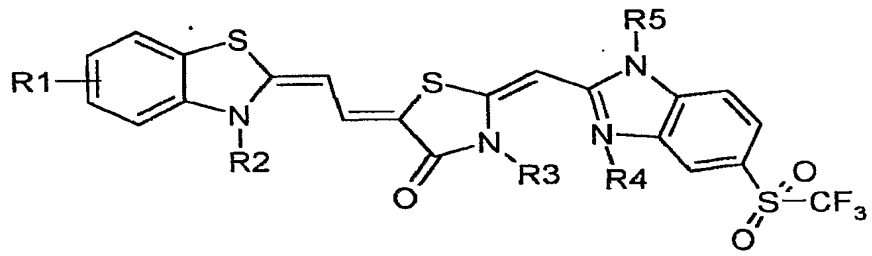
According to certain preferred embodiment the present invention provides

compositions comprising compounds of formula VI selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium (2324-0379)

3-(carboxymethyl)-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

R_5 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, aryl, optionally substituted on the aryl ring

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl;

According to another embodiment, R_1 is selected from the group consisting of 5-cyano, 5,6-dicyano, 5-methoxy, 5,6-dimethoxy, 6-chloro;

According to one embodiment, R_2, R_3 and R_4 are selected from the group consisting of methyl, ethyl, hydroxyethyl;

According to one embodiment R_5 is selected from the group consisting of methyl, ethyl, hydroxyethyl;

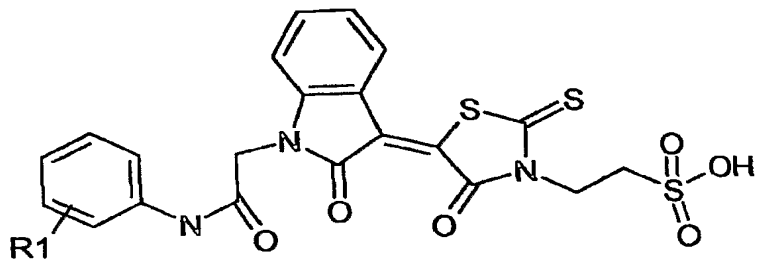
According to another embodiment R_5 is selected from the group consisting of phenyl, 4-methylphenyl, 3-methoxyphenyl.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VII selected from:

3-ethyl-2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-thiazolidinylidene]methyl] –1-phenyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-1,3-diethyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl;

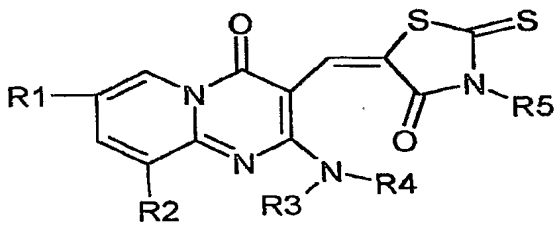
According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl;

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VIII selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid (Compound No. 11)

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to some aspects the present invention provides a method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

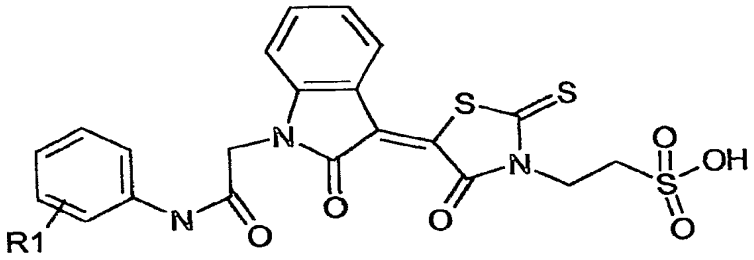
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No. 125).

Certain Inhibitor Compounds of general formula IX interact directly with GAGs, see Example 7. Examples are Inhibitor Compounds nos.110 and 125 that are described in Table 2.

According to another aspect, the present invention provides a method for the treatment or prevention of Varicella Zoster Virus infection, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a

therapeutically effective amount of a compound of the formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

According to one embodiment, R_1 is selected from the group consisting of methyl, ethyl, hydroxyethyl,

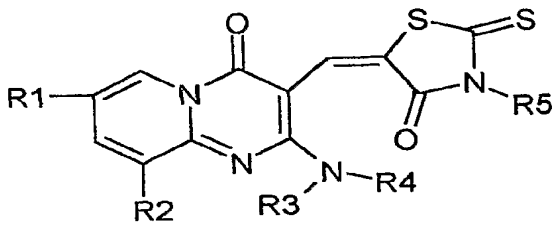
According to another embodiment, R_1 is selected from the group consisting of halogen, cyano, 3,4-dicyano, methoxy, 4,5-dimethoxy, 3-trifluoromethyl

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula VIII selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

According to another aspect, the present invention provides a method for the treatment or prevention of hepatitis C infection, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the general formula IX:



I

wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

According to certain preferred embodiment the present invention provides compositions comprising compounds of formula IX selected from:

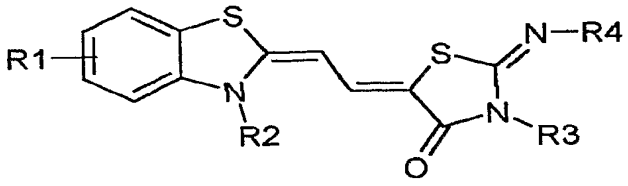
4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)- (Compound No. 110)

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl- (Compound No. 126);

4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]- (Compound No. 125).

According to some aspects the present invention provides a method for the

treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG - GBVP interactions, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

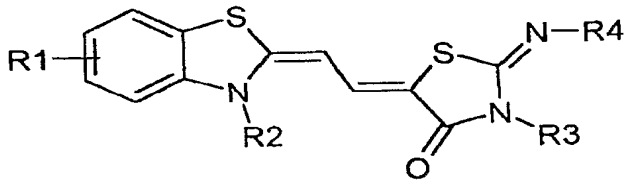
R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides a method of teatment with the following compound of formula X:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. 102).

According to another aspect, the present invention provides a method for the treatment or prevention of hepatitis C infection, comprising the step of administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a compound of the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

According to certain preferred embodiment the present invention provides a method of treatment hepatitis C with the following compound of formula X:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. **102**).

In a particular embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable

solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration.

According to one embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits GAG-GBVP binding by interacting with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

According to one currently preferred embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits GAG-GBVP binding by interacting with HS-GAG or heparin or derivatives and oligosaccharide fragments thereof.

According to another embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits the interaction of GAGs with GAG specific GBVPs selected from the group consisting of CMV envelope glycoprotein B, etc.

According to one currently preferred embodiment, the pharmaceutical composition comprises an Inhibitor Compound that inhibits the interaction of GAGs with CMV envelope glycoprotein B.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure description of how to make the assays, the assay components, and carry out the assays of the invention and are not intended to limit the scope of what is regarded as the invention.

EXAMPLES

Example 1: An assay for CMV envelope glycoprotein B binding to immobilized heparin that is suitable for screening of compound collections.

Porcine intestinal mucosa heparin conjugated to Bovine Serum Albumin (Heparin-BSA; Sigma Cat.No.H0403) at 5mg/ml in Phosphate Buffered Saline (PBS; pH6.5) was added to a 96 well polystyrene ELISA plate (NUNC Cat. No. 442404; 0.1ml per well) and incubated Over Night (ON) at 4 C. Following the incubation the plate was washed consecutively, by immersion, with de-ionised water and PBS (pH-6.5). The ELISA plate was then blocked with BSA (ICN Cat.No.160069, 3%, 200 µl per well) for 1 hour at Room Temperature (RT). Following blocking, the plate was washed with de-ionized water then PBS (pH 6.5) plus Tween 20 (0.05%). CMV envelope glycoprotein B (Research Diagnostics, INC. Cat.No.RDI-RCMVAG-B) dissolved in PBS (supplemented with BSA (0.1%)) was added to the ELISA plate (100ul per well) and incubated for 60 minutes at RT with shaking. Following incubation, the plate was washed with de-ionized water and with PBS (pH 6.5) plus Tween. Mouse anti-human Cytomegalovirus gB antibody (Research Diagnostics, INC. Cat.No. RDI-CMVG Babm) diluted in PBS (supplemented with BSA(0.1%)), 1:2000, was added to the ELISA plate (100ul per well) and incubated for 90 minutes at RT with shaking. Following the incubation, the plate was washed with de-ionised water and PBS (pH6.5) plus Tween. Goat anti-Mouse IgG (H&L) Peroxidase Conjugated antibody (Chemicon International, Inc. Cat.No. AP124P) diluted in PBS (supplemented with BSA (0.1%)), 1:1000, was added to the ELISA plate (100ul per well) and incubated for 30 minutes at RT with shaking. Following the incubation, the plate was washed with de-ionized water and with PBS (pH6.5) plus Tween. The peroxidase substrate cromogen, TMB (Dako Cat. No. S1599) was added (100µl per well) to the ELISA plate and incubated at room temperature. After 15 minutes ELISA Stop Solution (hydrochloric acid 1N, sulfuric acid 3N) was added (200ul per well) to stop the peroxidase catalyzed colorimetric reaction. The Optical Density of the samples was measured at 450nm using an ELISA plate reader (Dynatech MR5000). A dose response histogram is shown in Figure 1.

Example 2: Inhibition of Human CMV envelope glycoprotein B Binding to Heparin by Soluble Heparin

Porcine intestinal mucosa heparin conjugated to Bovine Serum Albumin (Heparin-BSA; Sigma Cat.No.H0403) at 5mg/ml in Phosphate Buffered Saline (PBS; pH6.5) was added to a 96 well polystyrene ELISA plate (NUNC Cat. No. 442404; 0.1ml per well) and incubated Over Night (ON) at 4 C. Following the incubation the plate was washed consecutively, by immersion, with de-ionised water and PBS (pH-6.5). The ELISA plate was then blocked with BSA (ICN Cat.No.160069, 3%, 200 µl per well) for 1 hour at Room Temperature (RT). Following blocking, the plate was washed with de-ionized water then PBS (pH 6.5) plus Tween 20. CMV envelope glycoprotein B (Research Diagnostics, INC. Cat.No.RDI-RCMVAG-B) dissolved in PBS (supplemented with BSA (0.1%)) was incubated, separately, with Heparin (Sigma Grade 1-A:From Porcine Intestinal Mucosa. Cat.No.H-3393). CMV envelope glycoprotein B (100ng/ml) was incubated with a range of Heparin concentrations (0.2-10mg/ml) in a final volume of 100ul, each concentration in duplicate for two hours at room temperature. Following the incubation, the samples were added to the BSA-blocked ELISA plate wells and incubated for two hours with shaking. Following incubation, the plate was washed with de-ionized water and PBS (pH 6.5) plus Tween. Mouse anti-human Cytomegalovirus gB antibody (Research Diagnostics, INC. Cat.No. RDI-CMVG Babm) diluted in PBS (supplemented with BSA(0.1%)), 1:2000, was added to the ELISA plate (100ul per well) and incubated for 90 minutes at RT with shaking. Following the incubation, the plate was washed with de-ionised water and PBS (pH6.5) plus Tween. Goat anti-Mouse IgG (H&L) Peroxidase Conjugated antibody (Chemicon International, Inc. Cat.No. AP124P) diluted in PBS (supplemented with BSA (0.1%)), 1:1000, was added to the ELISA plate (100ul per well) and incubated for 30 minutes at RT with shaking. The peroxidase substrate cromogen, TMB (Dako Cat. No. S1599) was added (100 µl per well) to the ELISA plate and incubated at room temperature. After 15 minutes ELISA Stop Solution (hydrochloric acid 1N, sulfuric acid 3N) was added (200 µl per well) to stop the peroxidase catalyzed colorimetric reaction. The Optical Density of the samples was measured at 450 nm using an ELISA plate reader (Dynatech MR5000).

A dose response curve of soluble heparin inhibition of CMV envelope glycoprotein B binding to immobilized heparin is shown in Figure 2.

Example 3: An assay for CMV envelope glycoprotein B binding to Glycosaminoglycans (GAGs) that is suitable for the screening of compound collections.

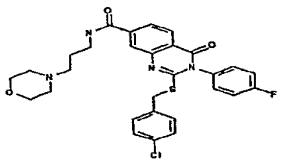
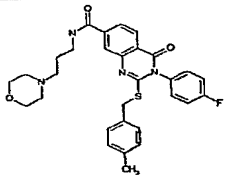
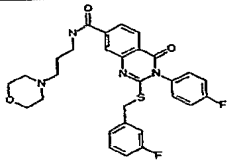
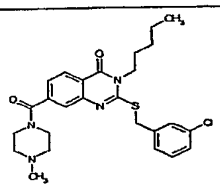
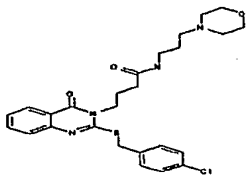
The GAGs, Bovine kidney Heparan Sulfate (HS-GAG), shark cartilage chondroitin sulfate, hog skin dermatan sulfate, bovine cornea keratan sulfate and low molecular weight heparins are commercially available (Sigma; Seikagaku Ltd, Japan). Human liver HS-GAG is purified as described (Dudas, J. et al., Biochem. J. 2000, 350, 245-251; Murata K., et al. 1985, Gastroenterology 89, 1248-1257). HS-GAG is conjugated to BSA to prepare a synthetic HS-GAG-BSA complex in which the HS-GAG is coupled via its reducing aldehyde terminus to the protein using sodium cyanoborohydride (Najjam, S. et al. 1997, Cytokine 12, 1013-1022). Other GAGs are coupled to BSA in a similar fashion. The CMV envelope glycoprotein B (GBVP) binding assay is similar to the one described in Example 1. In brief, HS-GAG-BSA is added to a 96 well polystyrene ELISA plate and incubated ON at 4°C. Following the incubation the plate is consecutively washed and blocked with BSA. GBVP, dissolved in PBS (supplemented with BSA (0.1%)) is added to the ELISA plate and incubated for 60 minutes at RT with shaking. Following incubation, the plate is washed, incubated with antibody, washed and finally TMB is added to the ELISA plate. After 15 minutes ELISA Stop Solution is added and the Optical Density of the samples is measured at 450 nm using an ELISA plate reader.

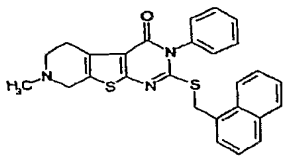
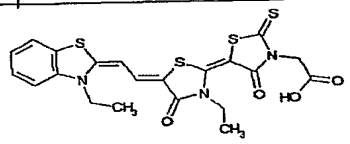
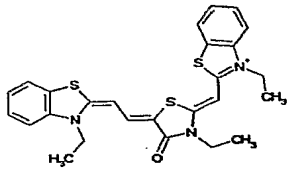
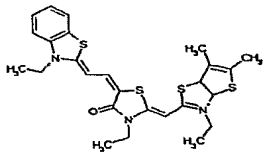
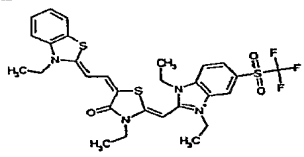
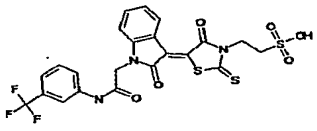
Example 4: A compound screening method - Contacting test compounds in the presence of heparin (or HS-GAG) and CMV envelope glycoprotein B, to identify Inhibitor Compounds.

The CMV envelope glycoprotein B (GBVP) binding assay described in Example 1 was used to screen a synthetic chemical compound collection on 96-well plates. The compound collection was purchased from ChemDiv Inc. (San Diego, CA). Compounds were dissolved in DMSO at 10mM final concentration and further diluted prior to assay. DMSO concentration in the screening well was up to 2%. Individual compounds at a final concentration of 30 μM were co-incubated with GBVP on plates containing immobilized heparin and following washing, bound GBVP was detected with anti-CMV GBVP antibody and secondary antibody conjugated to horseradish

peroxidase, as described in Example 1. Following color development, the % inhibition compared to control (no compound) for every compound was determined. Compounds that inhibited at least 30% of the signal were scored as hits. Examples of Inhibitor Compounds are listed in Table 1.

Table 1. Inhibition of CMV envelope glycoprotein B binding to heparin by selected Inhibitor Compounds.

Compound No.	Structure	% Inhibition at 30μM	% Inhibition at 100μM
1		33	
2			86
3		85	88
4		79	
5		86	

6		87	79
7		71	
8		99	
9		90	
10		61	
11		70	

Example 5: A compound screening method using the entire CMV envelope to identify inhibitors of the interaction between Heparan Sulfate (HS) GAGs and envelope glycoprotein B (and the envelope of other GAG-binding viruses)

Human CMV (HCMV) envelopes are prepared according to the method of (Britt WF and Mach M, 1996, Intervirology 39(5-6):401-12). Heparin-BSA (Sigma Cat. No. H0403) 5mg/ml in PBS is added to a 96 well polystyrene ELISA plate and incubated ON at 4°C. Following the incubation the plate is washed consecutively, by immersion, with de-ionized water and PBS. The ELISA plate is then blocked with BSA (3%, 200µl per well) for 1 hour at RT. Following blocking, the plate is washed with de-ionized water and PBS. Compounds are dissolved in DMSO at 10mM concentration, diluted and added to the individual wells at a final concentration of 30 µM. The viral envelope suspension (in PBS) is then incubated in the ELISA plate. Following incubation the plate is washed with PBS. Mouse anti-human Cytomegalovirus gB antibody (Research Diagnostics, INC. Cat.No. RDI-CMVG Babm) diluted in PBS (supplemented with BSA(0.1%)), 1:2000, is added to the ELISA plate (100ul per well) and incubated for 90 minutes at RT with shaking. After incubation the plate is washed twice with PBS then incubated with Goat Anti Mouse IgG Peroxidase Conjugated Antibody (Chemicon International, Cat. No. AP124P, 1:5000 dilution with PBS, plus BSA (0.1%)) for 30 minutes at 4°C. Following incubation, the plate is washed with PBS. The peroxidase substrate cromogen, TMB is added (100 µl per well) to the ELISA plate and incubated at RT. After 15 minutes ELISA Stop Solution was added (200 µl per well) to stop the peroxidase catalyzed colorimetric reaction. The Optical Density of the samples is measured at 450nm using an ELISA plate reader (Dynatech MR5000).

Example 6: A compound screening method using the entire Cytomegalovirus to identify inhibitors of the interaction between cell surface Heparan Sulfate (HS) GAGs and viral particles.

Human CMV virions (or other GAG-binding viral particles) are prepared according to the method of (Baldick CJ, Shenk T, 1996, J Virol 70(9):6097-105). Heparin-BSA (Sigma Cat. No. H0403) 5mg/ml in PBS is added to a 96 well polystyrene ELISA plate and incubated ON at 4°C. Following the incubation the plate is washed consecutively, by immersion, with de-ionized water and PBS. The ELISA

plate is then blocked with BSA (3%, 200µl per well) for 1 hour at RT. Following blocking, the plate is washed with de-ionized water and PBS. Compounds are dissolved in DMSO at 10mM concentration, diluted and added to the individual wells at a final concentration of 30 µM. The viral particle suspension (in PBS) is then incubated in the ELISA plate. Following incubation the plate is washed with PBS. Mouse anti-human Cytomegalovirus gB antibody (Research Diagnostics, INC. Cat.No. RDI-CMVG Babm) diluted in PBS (supplemented with BSA(0.1%)), 1:2000, is added to the ELISA plate (100ul per well) and incubated for 90 minutes at RT with shaking. After incubation the plate is washed twice with PBS then incubated with Goat Anti Mouse IgG Peroxidase Conjugated Antibody (Chemicon International, Cat. No. AP124P, 1:5000 dilution with PBS, plus BSA (0.1%)) for 30 minutes at 4°C. Following incubation, the plate is washed with PBS. The peroxidase substrate cromogen, TMB is added (100 µl per well) to the ELISA plate and incubated at RT. After 15 minutes ELISA Stop Solution was added (200µl per well) to stop the peroxidase catalyzed colorimetric reaction. The Optical Density of the samples is measured at 450nm using an ELISA plate reader (Dynatech MR5000).

Example 7: An assay to demonstrate direct interaction of Inhibitor Compounds with heparin and other HS-GAGs.

In order to demonstrate that Inhibitor Compounds indeed bind directly to heparin and other HS-GAGs, individual compounds are incubated with immobilized heparin in the absence of GBVP. 96 well ELISA plates are coated with Heparin-BSA, then blocked with BSA as described in Example 1. GBVP Hit Compounds, at final concentration 0.1-200µM, are incubated in the ELISA plate for 90 min, and then washed with incubation buffer. After washing, GBVP is added to the wells pre-incubated with compounds. At the same time, in separate control wells, GBVP is co-incubated with Hit Compounds for 90min. Following the incubation, GBVP bound to the plate is quantified by antibody conjugated to Horse Radish Peroxidase and OD measurement as described in Example 1. Examples of Inhibitor Compounds that interact directly with heparin are listed in Table 2.

Table 2: Direct Binding of Inhibitor Compounds to Heparin

Compound Number	Inhibition (%) Pre-Incubation	Inhibition (%) Co-incubation
110	73	80
1313	89	95
125	89	67

Example 8: Inhibition of Varicella Zoster Virus Infectivity by Inhibitor Compounds

Cytopathic Effect (CPE) inhibition assays were performed on Varicella Zostra Virus (VZV) as follows. Low passage Human Foreskin Fibroblast (HFF) cells were seeded into 96 well tissue culture plates 24h prior to use at a cell concentration of 2.5×10^5 cells per ml in 0.1ml of MEM supplemented with 10% FBS. The cells were then incubated for 24h at 37C in a CO_2 incubator. After incubation, the medium was removed and 125µl of experimental drug was added to the first row in triplicate wells, all other wells containing 100µl of media. The drug in the first row of wells was then diluted serially 1:5 throughout the remaining wells by transferring 25µl using the Cetus Liquid Handling Machine. After dilution of drug, 100µl of the virus (2500 PFU per well) was added to each well, excluding cell control wells, which received 100µl of MEM. The plates were then incubated at 37C in a CO_2 incubator for ten days. After the incubation period, media was aspirated and the cells stained with a 0.1% crystal violet solution for four hours. The stain was then removed and the plates rinsed using tap water until all excess stain was removed. The plates were allowed to dry for 24h and then read on a BioTek Plate reader at 620nm. Virus plaque numbers were used to determine the drug concentration required to inhibit viral replication by 50%, the Effective Concentration 50 (EC50). Acyclovir (ACV) was used as a positive control drug.

A Neutral Red Uptake Assay was employed to determine the drugs' cytotoxicity. Twenty-four hours prior to the assay, HFF cells were plated into 96 well plates at a concentration of 2.5×10^4 cells per well. After 24h, the media was aspirated and 125µl of drug was added to the first row of wells and then diluted serially 1:5 using the Cetus Liquid Handling as in the CPE assay. After drug addition, the plates

were incubated for seven days in a CO_2 incubator at 37C. At this time the media/drug was aspirated and 200µl/well of 0.01% neutral red in PBS was added and the plates incubated in the CO_2 incubator for one hour. The dye was aspirated and the cells washed using a Nunc Plate Washer. After removing the PBS, 200µl/well of 50% ETOH/1% glacial acetic acid (in H_2O) was added. The plates were rotated for 15 minutes and the optical densities (OD) read at 540nm on a plate reader. The OD540nm readings were used to determine the drug concentration required to inhibit 50% of stationary cells to take up neutral read, the Cytotoxic Concentration 50 (CC50). (CPE and CC assays Reference: Kern, ER. "Laboratory Procedures for Determining Antiviral Efficacy and Toxicity Against Herpesviruses and Orthopoxviruses". Antiviral Research Laboratory. The University of Alabama at Birmingham, Department of Pediatrics, Division of Clinical Virology, BBRB 309; 1530 3rd Avenue South, Birmingham, AL 35294-2170.)

It was found that Inhibitor Compound No.110 had an EC50 = 3.2 µg/ml in the CPE inhibition assay (ACV EC50 = 0.37µg/ml) and a CC50 = 11.8µg/ml in the cytotoxicity assay. It was found that Inhibitor Compound No.11 had an EC50 <0.03 µg/ml (ACV EC50 = 0.04µg/ml) and a CC50 > 100µg/ml.

Example 9: Inhibition of Hepatitis C Virus

Anti-viral activity of the compounds was determined in a primary *in vitro* anti-HCV assay using the stably HCV RNA-replicating cell line, AVA5, derived by transfection of the human hepatoblastoma cell line, Huh7 (Blight, et al., 2000, Science 290; 1972). Compounds were added to dividing cultures once daily for three days (media changed with each addition of compound). Cultures generally started the assay at 50% confluence and reached confluence during the last day of treatment. HCV RNA and cellular β-actin RNA levels were assessed 24 hours after the last dose of compound using dot blot hybridization. Assays were conducted using a single dose of test compound (in triplicate cultures). A total of 6 untreated control cultures, and triplicate cultures treated with 10IU/ml of α-interferon (the approximate EC_{90} with no cytotoxicity) and 100mM of ribavirin (the approximate CC_{90} with no antiviral activity) serve as positive antiviral and toxicity controls.

Both HCV and β-actin RNA levels in the treated cultures are expressed as a percentage of the mean levels of RNA detected in untreated cultures. β-actin RNA levels are used both as a measure of toxicity and to normalize the amount of cellular RNA in each sample. A level of 30% or less HCV RNA (relative to control cultures) is considered to be a positive antiviral effect, and a level of 50% or less β-actin RNA (relative to control cultures) is considered to be a cytotoxic effect.

It was demonstrated that Inhibitor Compounds Nos. 102, 110, 125 and 126 had excellent anti-HCV activity. The anti-hepatitis C virus and cytotoxicity activities of these Inhibitory Compounds were as follows:

Compound No.	Anti-Virus (%)	Cytotoxicity (%)
102	16	61
110	23	62
125	9.6	65.3
126	10.6	63.5

Inhibitor Compound **126** was tested on Bovine Viral Diarrhea Virus in MDBK cells and displayed excellent activity, $EC_{50} = 6\mu M$ ($IC_{50} > 100\mu M$, SI >17). Bovine Viral Diarrhea Virus is related to HCV and may serve as a "surrogate" virus to estimate range of action.

CLAIMS

1. A method of screening for small organic molecules that directly inhibit the interaction of GAGs with GBVPs, the method comprising the steps of:
   a. contacting a GAG with an GBVP in the presence of at least one candidate compound;
   b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as Inhibitor Compound, inhibiting GAG-GBVP interaction.
2. A method of screening for small organic compounds that directly inhibit

the interaction of GAGs with GBVPs, the method comprising the steps of:

a. contacting a GAG with at least one small organic compound;

b. removing of unbound organic compound;

c. adding a GBVP; and

measuring the amount of the GAG bound to the GBVP or the amount of the GBVP bound to the GAG, wherein a significant decrease in GAG-GBVP binding for the GAG contacted with the organic compound as compared to GAG-GBVP binding for said GAG not contacted with the compound identifies said compound as Inhibitor Compound inhibiting GAG-GBVP interaction.

3. The method according to claims 1-2, wherein the GBVP is a fusion protein.

4. The method according to claims 1-2, wherein the GAG or the GBVP is tagged or labeled.

5. The method according to claim 4 wherein the label is selected from the group consisting of a dye, a fluorescent dye, a chemoluminescent agent or a radioactive agent.

6. The method according to claim 4 wherein the GBVP is tagged by an antibody.

7. The method according to claims 1-2, wherein the GAG is selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

8. The method according to claim 7, wherein the GAG is heparan sulfate (HS-GAG) or heparin.

9. The method according to claims 1-2 wherein the small organic molecules are contacted with proteoglycan containing GAG.

10. The method according to claim 9 wherein the proteoglycan containing GAG is heparan-sulfate proteoglycan (HS-PG).

11. The method according to claims 1-2, wherein the GBVP is selected from the group consisting of CMV envelope glycoprotein B, hepatitis C envelope glycoprotein E2, HIV glycoprotein gp120 and HIV gp41.

12. The method according to claim 11 wherein the GBVP is CMV envelope glycoprotein B.

13. The method according to claims 1-2 wherein small organic molecules are contacted with whole live virus.

14. A compound identified according to any one of claims 1-13.

15. A pharmaceutical composition comprising as an active ingredient an Inhibitor Compound identified by a screening method comprising the steps of:

a. contacting a GAG with a GBVP in the presence of at least one candidate compound;

b. measuring the amount of GAG bound to GBVP or the amount of GBVP bound to GAG, wherein a significant decrease in GAG-GBVP binding as compared to GAG-GBVP binding not in the presence of the candidate compound identifies said compound as Inhibitor Compound, inhibiting GAG-GBVP interaction,

further comprising a pharmaceutically acceptable diluent or carrier.

16. The pharmaceutical composition according to claim 13 wherein the Inhibitor Compound inhibits GAG-GBVP binding by interacting with GAGs selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

17. The pharmaceutical composition according to claim 13 wherein the Inhibitor Compound inhibits the interactions of GAG with GAG specific GBVP selected from the group consisting of CMV envelope glycoprotein B, etc.

18. The pharmaceutical composition according to claim 15 wherein the GBVP is CMV envelope glycoprotein B.

19. A method for inhibiting virus attachment and entry comprising the step of exposing the cells to a small organic molecule that interacts directly with at least one GAG in an amount sufficient for preventing the interactions of the GAG with at least one GBVP.

20. The method according to claim 17 wherein virus attachment and entry is inhibited in vitro.

21. The method according to claim 17 wherein virus attachment and entry is inhibited in vivo.

22. The method according to claim 17 wherein virus attachment and entry is

inhibited by the interaction of the small organic molecule with GAG selected from the group consisting of heparan sulfate (HS-GAG), heparin, chondroitin sulfate, dermatan sulfate, keratan sulfate and derivatives and fragments thereof.

23. The method according to claim 20 wherein the GAG is heparan sulfate (HS-GAG) or heparin or oligosaccharide fragments thereof.

24. The method according to claim 20 wherein the GAG is a part of proteoglycan.

25. The method according to claim 22 wherein the proteoglycan is heparan-sulfate proteoglycan (HS-PG).

26. The method according to claim 17 wherein the small organic molecule inhibits the interactions of GAG with GAG specific GBVP selected from the group consisting of CMV envelope glycoprotein B, etc.

27. The method according to claim 24 wherein the GBVP is CMV envelope glycoprotein B.

28. The method according to any one of claims 17-25 wherein the small organic compound is administered for the treatment or prevention of a viral disorder, infection or disease.

29. The method according to claim 26 wherein the viral disorder, condition or process is selected from the group consisting of HIV, HSV, CMV, etc.

30. A method for the treatment or prevention of disorders related to virus attachment and entry comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 12 that directly inhibits the interaction of GAGs with GBVPs, preventing virus attachment and entry mediated by the GAG.

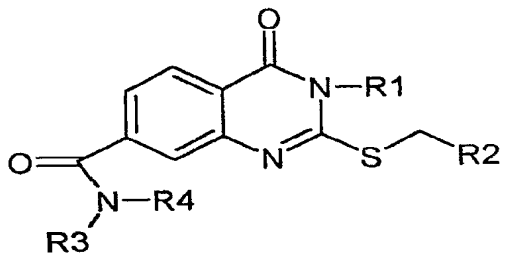
31. The method according to claim 28 wherein the disorder related to virus attachment and entry is selected from the group consisting of influenza, etc.

32. The method according to claim 29 wherein the disorder is a bacterial infection.

33. The method according to claim 29 wherein the infections disease is a parasite induced disease.

34. The method according to claim 32 wherein the parasite induced disease is malaria.

35. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula I:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 and R_4 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

36. The pharmaceutical composition according to claim 35, wherein compound of formula I is selected from:

2-[[(4-chlorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-methylphenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(3-fluorophenyl)methyl]thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[(2-oxo-2-phenylethyl)thio]-3-(4-fluorophenyl)-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide

2-[[(4-oxo—4H-pyrido[1,2-a]pyrimidin-2-yl)methyl]thio]-3-(2-furanylmethyl)-3,4-dihydro-4-oxo-N-(2-methoxyethyl)-7-quinazolinecarboxamide

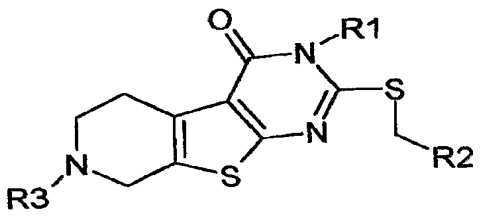
2-[(2-oxo-2-phenylethyl)thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(1-piperidinyl)propyl]-7-quinazolinecarboxamide

4-[[3,4-dihydro-4-oxo-3-pentyl-2-[(4-pyridinylmethyl)thio]-7-quinazolinyl]carbonyl]-1-piperazinecarboxylic acid ethyl ester

2-[[2-[[(3-chlorophenyl)methyl]thio]-3-pentyl-3,4-dihydro-4-oxo-N-(4-methylpiperazinyl)-7-quinazolinecarboxamide

2-[[2-oxo-2-(4-fluorophenyl)ethyl]thio]-3-[(tetrahydro-2-furanyl)methyl]-3,4-dihydro-4-oxo-N-[3-(4-morpholinyl)propyl]-7-quinazolinecarboxamide.

37. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula II:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

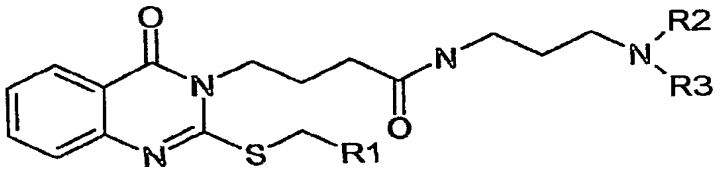
R_2 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;

R_3 is selected from the group consisting of hydrogen; linear or branched chain C1-C6 loptionally substituted alkyl; arylalkyl, optionally substituted at the aryl group;

cycloalkyl, optionally substituted with alkyl groups; alkanoyl; arylcarbonyl, optionally substituted at the aryl group; cycloalkylcarbonyl; alkoxycarbonyl; and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

38. The pharmaceutical composition according to claim 37, wherein compound of formula II is selected from:
3-(4-ethoxyphenyl)-2-[[(4-fluorophenyl)methyl]thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one
3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-methyl-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one
3-phenyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(2-phenylethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one
3-cyclohexyl-2-[(1-naphthalenylmethyl)thio]-5,6,7,8-tetrahydro-7-(phenylmethyl)-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4(3H)-one.

39. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula III:



wherein:
R_1 is selected from the group consisting of aryl, optionally substituted on the aryl ring, fused ring aryl, arylcarbonyl, optionally substituted on the aryl ring, heteroaryl, heteroarylcarbonyl;
R_2 and R_3 are selected from the group consisting of hydrogen linear or branched chain C1-C6 alkyl, optionally substituted by alkoxy group or by 5-7 membered heterocyclyl ring containing one or two heteroatoms, the alkyl groups may form (un)substituted 5-

7 membered saturated heterocyclyl ring containing one or two nitrogens, optionally substituted on the nitrogen atoms;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

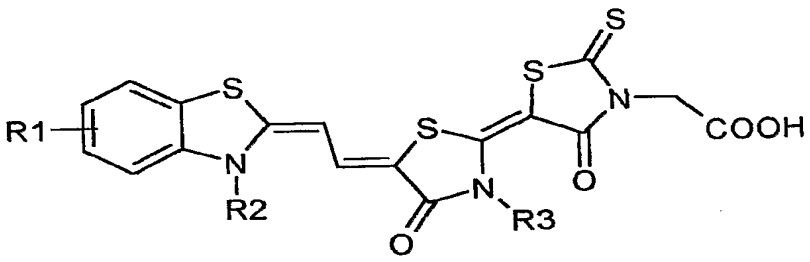
40. The pharmaceutical composition according to claim 39, wherein compound of formula III is selected from:

2-[[(4-chlorophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(2-bromophenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

2-[[(1-naphthalenyl)methyl]thio]-N-[3-(4-morpholinyl)propyl]-4-oxo-3(4H)-quinazolinebutanamide

41. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IV:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl,, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

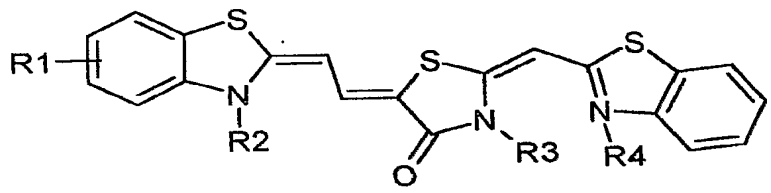
42. The pharmaceutical composition according to claim 41, wherein compound of formula IV is selected from:

5-[3-ethyl-5-[(3-ethyl-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-ethyl-5-[(3-ethyl5,6-dimethoxy-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

5-[3-(carboxymethyl) -5-[[5-cyano-3-(2-hydroxyethyl)-2-(3H)-benzothiazolydene)ethylidene]-4-oxo-2-thiazolidinylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid

43. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula V:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

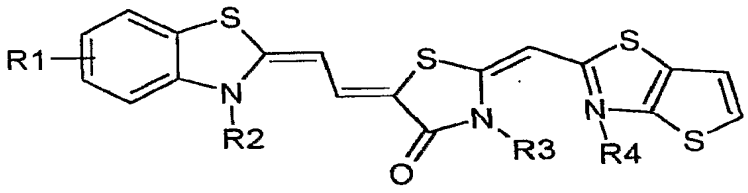
44. The pharmaceutical composition according to claim 43, wherein

compound of formula V is selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] benzothiazolium (1313-0069)

2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-3,6-dimethyl-benzothiazolium

45. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VI:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

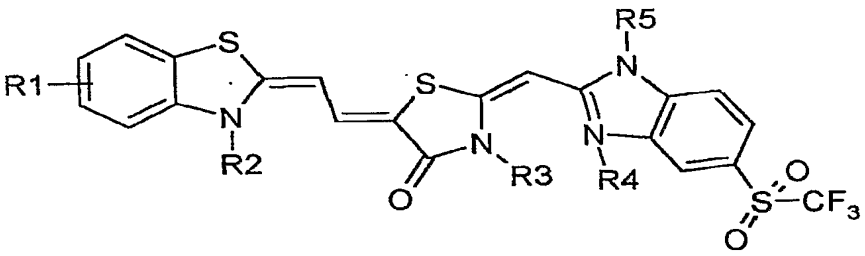
and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

46. The pharmaceutical composition according to claim 45, wherein compound of formula VI is selected from:

3-ethyl-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium (2324-0379)

3-(carboxymethyl)-2-[[4-oxo-3-ethyl-5-[[3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl] –6,7-dimethyl-thieno[2,3-d]thiazolium

47. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2, R_3 and R_4 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group.

R_5 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, aryl, optionally substituted on the aryl ring

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

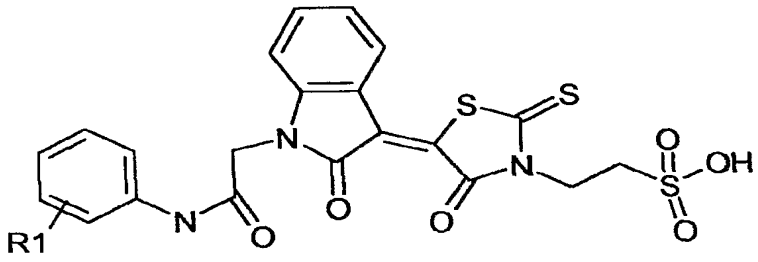
48. The pharmaceutical composition according to claim 47, wherein compound of formula VII is selected from:

3-ethyl-2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-thiazolidinylidene]methyl] –1-phenyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

2-[[3-ethyl-4-oxo-5-[(3-ethyl-2(3H)-benzothiazolylidene]ethylidene]-2-thiazolidinylidene]methyl]-1,3-diethyl-5-[(trifluoromethyl)sulfonyl]-1H-benzimidazolium

49. A method for the treatment or prevention of diseases and disorders related to virus attachment and entry mediated by GAG-GBVP interactions, comprising the step of administering to a subject in need

thereof a pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula VIII:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

and pharmaceutically acceptable salts thereof; further comprising a pharmaceutically acceptable diluent or carrier.

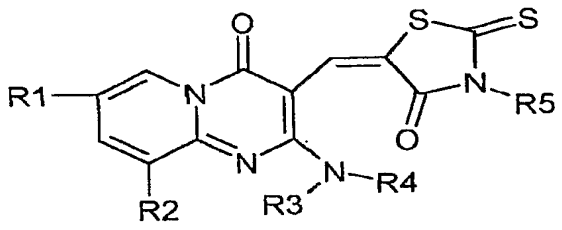
50. A method according to claim 49 wherein the compound of formula VIII is selected from:

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[[3-(trifluoromethyl)phenyl]amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid

5-[1,2-dihydro-2-oxo-1-[2-oxo-2-[3-(cyanophenyl)amino]ethyl]-3H-indol-3-ylidene]-4-oxo-2-thioxo-3-thiazolidineethanesulfonic acid.

or carrier.

51. A pharmaceutical composition comprising a therapeutically effective amount of at least one molecule having the general formula IX:



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wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

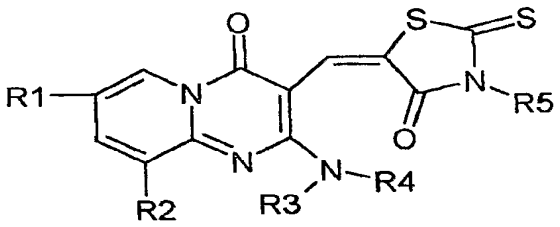
52. A method according to claim 51 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)-.

53. A method according to claim 51 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl-.

54. A method according to claim 51 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]-. methyl-.

55. A method for the treatment or prevention of hepatitis C virus infection, comprising the step of administering to a subject in need thereof a a therapeutically effective amount of at least one molecule having the

general formula XI:



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wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

56. A method according to claim 55 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)-.

57. A method according to claim 55 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl-.

58. A method according to claim 55 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]-. methyl-.

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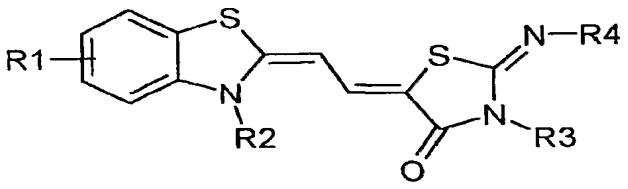
59. A pharmaceutical composition comprising a therapeutically effective

amount of at least one molecule having the general formula X:



wherein:

R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

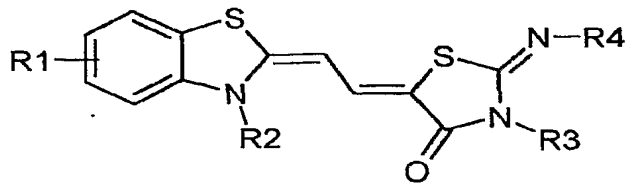
R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

60. A pharmaceutical composition according to claim 59, wherein compound of formula X is:

5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. **102**).

61. A method for the treatment or prevention of hepatitis C virus infection, comprising the step of administering to a subject in need thereof a therapeutically effective amount of at least one molecule having the general formula X:



wherein:

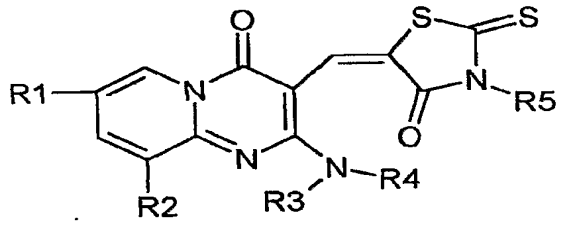
R_1 is selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group, alkoxy, cyano, halogen, cycloloalkyl, arylalkyl, aryl, optionally substituted on the aryl ring, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl;

R_2 and R_3 are selected from the group consisting of linear or branched chain C1-C10 alkyl optionally substituted on the alkyl group;

R_4 is selected from the group consisting of arylalkyl, aryl, optionally substituted on the aryl ring, , heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl.

62. A method according to claim 61 wherein the compound of formula X is: 5-[(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-3-methyl-2-[(phenylmethyl)imino]-4-thiazolidinone (Compound No. **102**).

63. A method for the treatment or prevention of Varicella Zoster Virus infection, comprising the step of administering to a subject in need thereof a therapeutically effective amount of at least one molecule having the general formula XI:



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wherein:

R_1 and R_2 are selected from the group consisting of hydrogen or straight chain or branched alkyls of 1-6 carbon atoms;

R_3 and R_4 are selected from the group consisting of C_1 –C_6 alkyl, cycloalkyl, aryl, arylalkyl optionally substituted at the alkyl group by piperidinyl, 4-morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-arylpiperazinyl, 4-arylalkylpiperazinyl, imidazolyl, or R_3 and R_4 together may form a 5 to 7 member saturated cycloalkyl or heterocyclyl

ring containing one or two heteroatoms and optionally substituted at the heterocyclic ring;

R_5 is straight chain or branched alkyl of 1-6 carbon atoms (optionally substituted by alkoxy, phenyl, 4-alkylphenyl, 4-alkoxyphenyl, 2-furanyl, tetrahydro-2-furanyl, 1,3-benzodioxol-5-yl), cycloalkyl, alkenyl;

and pharmaceutically acceptable salts thereof, further comprising a pharmaceutically acceptable diluent or carrier.

64. A method according to claim 63 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-butyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-9-methyl-2-(4-methyl-1-piperazinyl)-.

65. A method according to claim 63 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[[3-(phenylmethyl)-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-[[2-(4-morpholinyl)ethyl]amino]-9-methyl-.

66. A method according to claim 63 wherein the compound of formula IX is 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[(3-phenylmethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-[[3-(1H-imidazol-1-yl)propyl]amino]-methyl-.

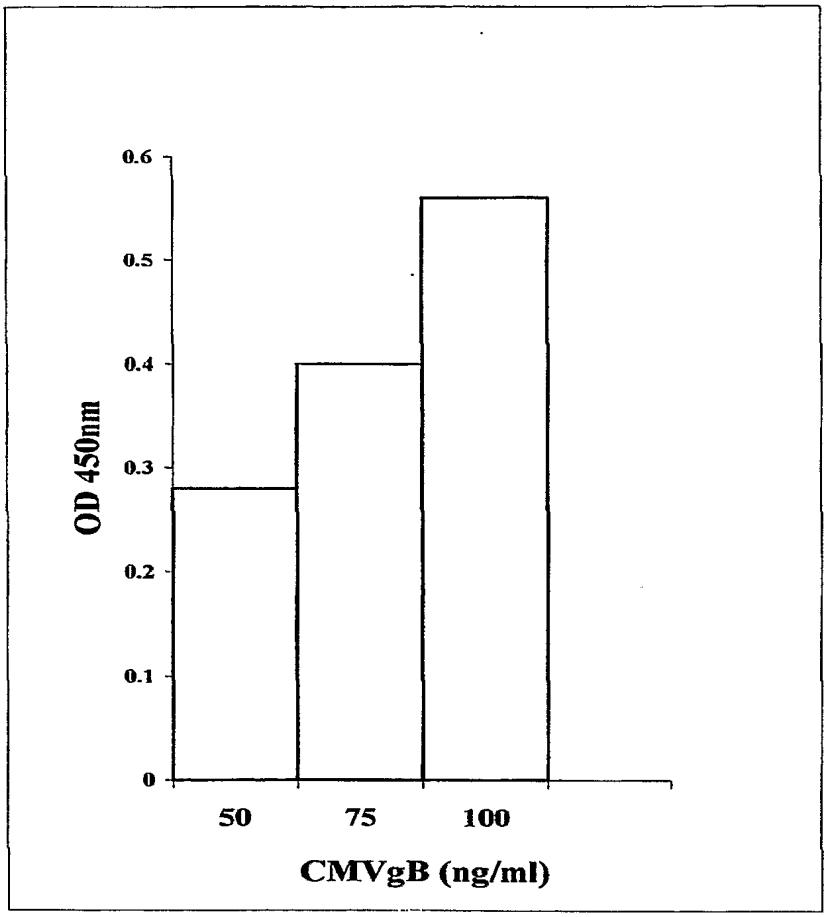

FIGURE 1

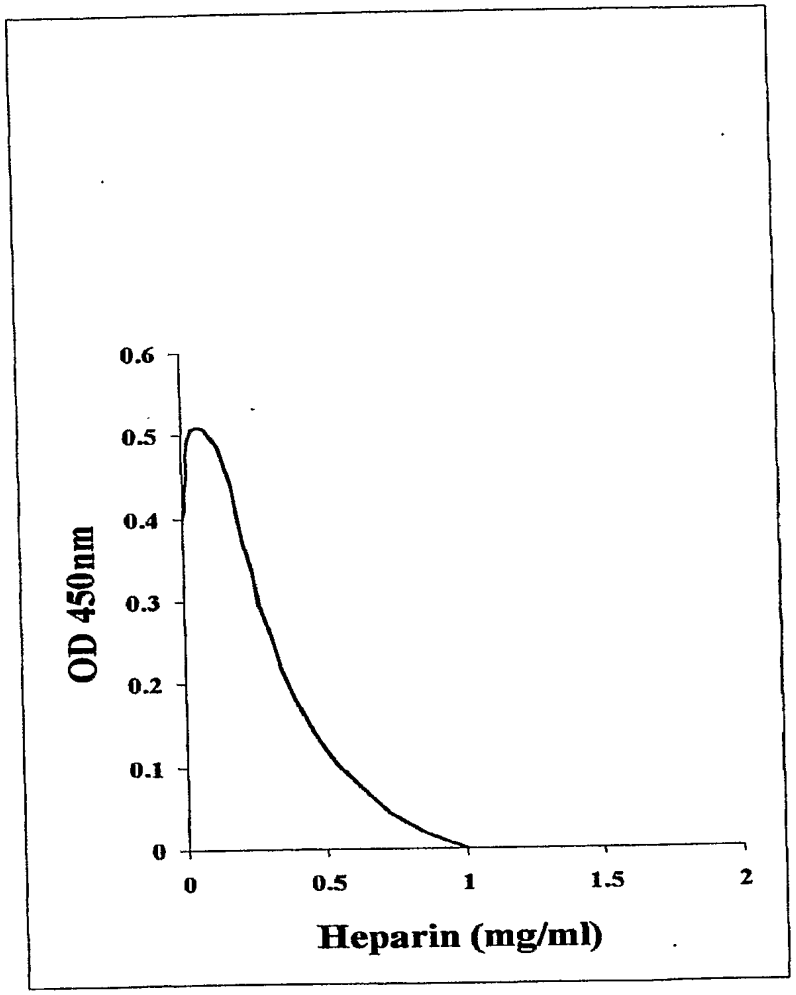

FIGURE 2